Total Synthesis of (+)-Discodermolide by Catalytic Stereoselective Borylation Reactions

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TOTAL SYNTHESIS OF (+)-DISCODERMOLIDE

BY

CATALYTIC STEREOSELECTIVE BORYLATION REACTIONS

a dissertation

by

ZHIYONG YU

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Dissertation Advisor:

James P. Morken

ABSTRACT: (+)-Discodermolide is a marine natural product and is one of the most potent microtubule stabilizers in human cell lines. Because of its unique linear structure and important properties, a number of total syntheses of (+)-discodermolide and its derivatives have been reported. Herein, an efficient, highly convergent, and stereocontrolled total synthesis is presented (Chapter 2). The synthesis relied on the development of three catalytic and stereoselective processes: platinum-catalyzed asymmetric diene diboration, nickel-catalyzed diastereoselective hydroboration of chiral dienes (Chapter 1), and nickel-catalyzed borylative diene-aldehyde coupling (see Chapter 4). Combination of these reactions allows preparation of the target in a short sequence. Moreover, the development of rhodium-catalyzed asymmetric hydroformylation (Chapter 3) makes this approach the first Roche ester free (+)-discodermolide synthesis.

To my wife, parents and family

whose love and support sustained me through out

and to my coming daughter

whose kicking and rolling never stopped amazing me

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Chinese festivals, I never stopped missing you. I am also thankful to the rest of my family for their encouragement and good times on the rare occasions I was able to visit in China.

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List of Abbreviations

Ac: acetate

Ac_2O: acetic anhydride

AcOH: acetic acid

Ar: aryl

BISBI: bis((diphenylphosphino)methyl)-1,1'-biphenyl

Bn: benzyl

$B_2(pin)_2$: bis(pinacolato) diboron

Bu: butyl

Bz: benzoyl

Bz_2O: benzoic anhydride

Cb: carbamate

CF_3: trifluoromethyl

cod: cyclooctadiene

Cy: cyclohexyl

dba: dibenzylidene acetone

CH_2Cl_2: dicholoethane

DIPEA: diisopropylethylamine

(−)-DIOP: (4*R*,5*R*)-4,5-Bis(diphenylphosphino-methyl)-2,2-dimethyl-1,3-dioxolane

DMF: dimethylformamide

DMAP: 4-(dimethylamino)pyridine

dppe: 1,2-bis(diphenylphosphino)ethane

dr: diastereomeric ratio

e.e.: enantiomeric excess

Et: ethyl

eq: equation

equiv: equivalent(s)

e.r.: enantiomeric ratio

Et_2O: diethyl ether

EtOAc: ethyl acetate

HB(pin): pinacolborane

HG-II: Hoveyda-Grubbs catalyst 2^{nd} generation

GC: gas chromatography

h: hour(s)

HMPT: hexamethylphosphorous triamide

HPLC: high performance liquid chromatography

KO*t*-Bu: potassium *tert*-butoxide

K-Selectride®: potassium tri-*sec*-butylborohydride

L: ligand

LAH: lithium aluminum hydride

LDA: lithium diisopropylamide

LUMO: lowest unoccupied molecular orbital

M: metal

*m*CPBA: 3-chloroperbenzoic acid

Me: methyl

μL: microliter

mg: milligram

mL: milliliter

mmol: millimole

$NaIO_4$: sodium periodate

n-BuLi: *n*-butyllithium

NEt_3: triethylamine

Nf: nonafluorobutane-1-sulfonic acid

Ni: nickel

NMO: *N*-methylmorpholino *N*-oxide

NMR: nuclear magnetic resonance

NOBIN: 2-amino-2'-hydroxy-1,1'-binaphthyl

npg: neopentylglycol

Nu: nucleophile

OBO: 4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octan-1-yl

PCy_3: tricyclohexylphosphine

Ph: phenyl

(*S*,*S*)-Ph-BPE: (+)-1,2-Bis((2*S*,5*S*)-2,5-diphenylphospholano)ethane

pin: pinacol

PMB: *para*-methoxybenzyl

PPTS: pyridinium *p*-toluenesulfonate

p-TsOH: *para*-toluenesulfonic acid

SFC: supercritical fluid chromatography

TADDOL: 2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol

TBAF: *tetra*-butyl ammonium fluoride

T-BDCP: *trans*-1,2-bis((diphenylphosphino)methyl)cyclopropane

TBDPS: *tert*-butyldiphenylsilyl

TBS: *tert*-butyldimethylsilyl

TBSOTf: *tert*-Butyldimethylsilyl trifluoromethanesulfonate

t-BuLi: *t*-butyllithium

TES: triethylsilyl

Tf: trifluoromethanesulfonate

THF: tetrahydrofuran

TLC: thin-layer chromatography

TMP: 2,2,6,6-tetramethylpiperidine

TMS: trimethylsilyl

TPAP: tetrapropylammonium perruthenate

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Chapter 1

Nickel-Catalyzed Diastereoselective 1,4-Hydroboration of Chiral 1,3-Dienols

1.1 Introduction

Polyketides are a class of secondary metabolites that often possess active bioactivity and useful pharmacological properties (selected examples shown in Figure 1.1).[1] One key characteristic of polyketides is the repeated presence of 1,3-oxygenation on the carbon backbone (highlighted in red in Figure 1.1), which is produced during the biosynthesis by decarboxylative condensation of malonic carboxylic acids followed by ketone reduction.[2] This process installs two carbons at one time and is repeated until an appropriate chain length is reached (Figure 1.2a). In the development of non-enzymatic syntheses of polyketides, a similar two-carbon installation process is also achieved by asymmetric aldol reaction with high selectivity, efficacy, and predictability (Figure 1.2b).[3]

---

[1] (a) *Macrolide Antibiotics. Chemistry, Biology, and Practice*, 2nd ed.; Omura, S., Ed.; Academic Press: New York, 2002. (b) Polyketides Biosynthesis, Biological Activity, and Genetic Engineering; Rimando, A. M., Baerson, S. R., Eds.; ACS Symposium Series 955; American Chemical Society: Washington, DC, 2007. (c) Newman, D. J.; Cragg, G. M. *J. Nat. Prod*. **2007**, *70,* 461. (d) Newman,D. J.; Grothaus, P.G.; Cragg, G. M. *Chem. Rev***. 2009**, *109*, 3012. (e) O'Hagan, D. *The Polyketide Metabolites*; Ellis Horwood: Chichester,U.K., 1991.

[2] For a review, see: J. Staunton, K. J. Weissman, *Nat. Prod. Rep*. **2001**, *18*, 380.

[3] (a) Schetter, B.; Mahrwald, R. *Angew. Chem. Int. Ed*. **2006**, *45*, 7506. For the first synthesis of erythromycin A see: (b) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E. Au-Yeung, B. W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H. *J. Am. Chem. Soc.* **1981**, *103*, 3215. For selected examples of related syntheses, see: (c) Martin, S. F.; Hida, T.; Kym, P. R.; Loft, M.; Hodgson, A. *J. Am. Chem. Soc*. **1997**, *119*, 3193. (d) Corey, E. J.; Kim, S.; Yoo, S.;

Figure 1.1. Selected Polyketide Natural Products

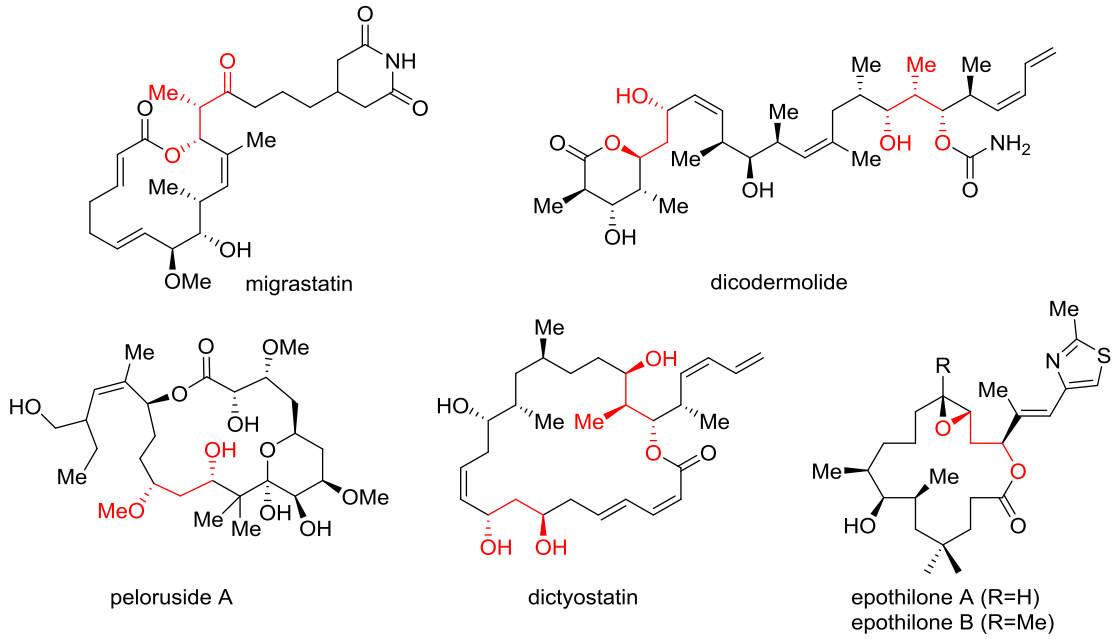
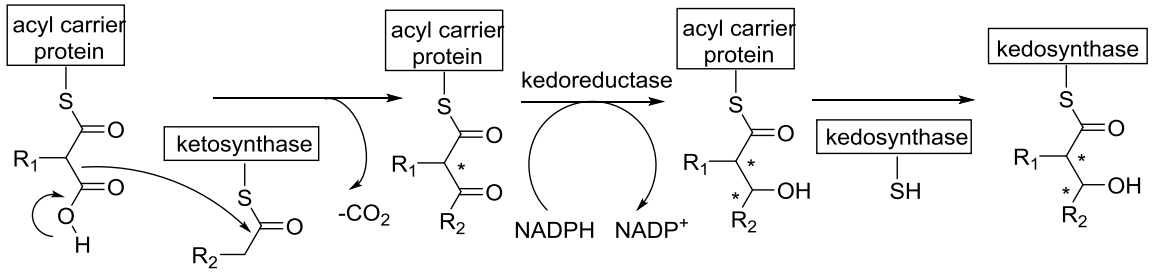
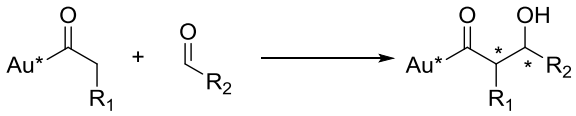


Figure 1.2. Biosynthesis and Chemical Syntheses of Polyketides

(a) biosyntheses



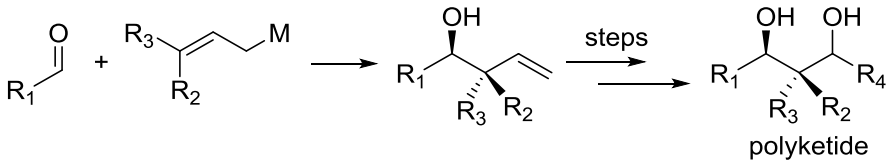
(b) chemical syntheses via aldol reactions



Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc*. **1978**, *100*, 4620. (e) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **1987**, *109*, 1565. (f) Myles, D. C.; Danishefsky, S. J. *J. Org. Chem*. **1990**, *55*, 1636. (g) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc*. **1998**, *120*, 5921. (h) Stang, E. M.; White, M. C. *Nat. Chem*. **2009**, *1*, 547. (i) Chandra, B.; Fu, D.; Nelson, S. G. *Angew. Chem. Int. Ed*. **2010**, *45*, 2591.

Although the aldol reaction has been widely used to construct β-hydoxy carbonyls for polyketide syntheses, a number of other useful methods have been developed as alternatives, such as allylation of carbonyls.[4] Asymmetric allylation of carbonyls is one of the most efficient methods to provide diastereo- and enantiomerically enriched homoallylic alcohols. Importantly, the associated versatile olefin can be converted to 1,3-dioxygenated motif that maps onto polyketide structures (Scheme 1.1).

Scheme 1.1. Allylation as an Important Tool for Polyketide Syntheses



Although the existing methods construct polyketides efficiently, there still remains a great need to develop creative methods to rapidly build the polyketide moiety. This chapter will focus on the development of a novel Ni-catalyzed diastereoselective 1,4-hydroboration of 1,3-dienols that delivers highly selective homoallylic alcohol derivatives for polyketide syntheses.

1.2 Background

1.2.1. Vinylogous Aldol Reactions for Polyketide Syntheses

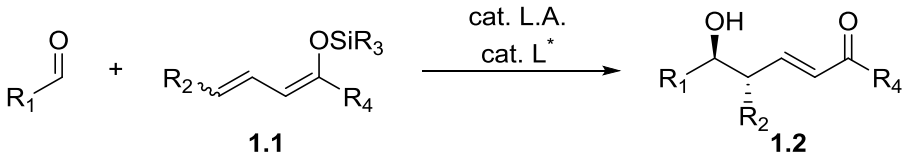
Despite the fact that decades of beautiful, powerful and profoundly influential chemistry have been devoted to the synthesis of polyketides, there still remains a great need to develop new methods to construct such structures "ideally".[5] For example, the

[4] For reviews, see: (a) Schinzer, D. *Synthesis* **1988**, 263. (b) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. (c) Hoffman, R. W. *Pure Appl. Chem.* **1988**, *60*, 123. For chiral allyl & allenyl silanes, see: (d) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. For enantioselective catalysis, see: (e) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774.

[5] Gaich, T.; Baran, P. S. *J. Org. Chem*. **2010**, *75*, 4657.

aldol reaction plays a very important role in ketide syntheses (Section 1.1), but separate multi-step transformations are required when the molecule contains unsaturation next to the propionate as shown in discodermolide and migrastatin (Figure 1.1). The vinylogous aldol has been developed to address this issue, which uses treatment of an extended enolate **1.1** with an aldehyde to generate a product with an adjacent olefin moiety (**1.2**) (Scheme 1.2). But, unfortunately, such vinylogous aldol reaction is only *anti*-selective and only highly enantioselective when aromatic aldehydes or α,β-unsaturated aldehydes are used.[6]

Scheme 1.2. Catalytic Asymmetric Vinylogous Aldol Reactions



1.2.2. Crotylation for Polyketide Syntheses and Preparation of Crotyl Metal Reagents

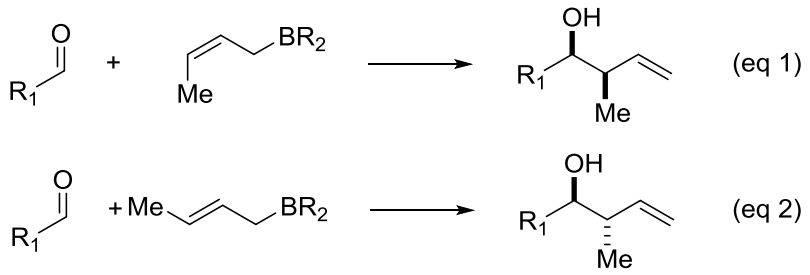
The ketide unit with adjacent unsaturation can also be prepared by addition of a crotyl metal reagent to a prochiral aldehyde, and this reaction can be accomplished with excellent stereo- and enantioselectivity.[7] For example, addition of a crotylboronate to an aldehyde furnishes *syn*- or *anti*-propionate motifs bearing adjacent olefin in one step (Scheme 1.3).

---

[6] (a) Denmark, S. E.; Heemstra Jr., J. R.; Beutner, G. L. *Angew. Chem. Int. Ed*. **2005**, *44*, 4682. (b) Brodmann, T.; Lorenz, M.; Schäckel, R.; Simsek, S.; Kalesse, M. *Synlett.* **2009**, 174.

[7] Reviews on catalytic asymmetric carbonyl allylation: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis, Supplement* Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds.; Springer-Verlag, Berlin, **2004**, *Vol. 2*, 97. (c) For selected recent examples: (e) Jain, P.; Antilla, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 11884. (f) Rauniyar, V.; Hall, D. G. *Angew.Chem. Int. Ed.* **2006**, *45*, 2426. (g) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (h) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660. (i) Kim, I. S.; Han, S. B.;Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2514. (j) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891.

Scheme 1.3. Examples of Carbonyl Crotylation



In addition to their relative non-toxicity,[8] another major advantage of crotylboron reagents is that *syn*- or *anti*-selectivity of crotylation is completely controlled by the configuration of the reagent (Scheme 1.3).[7a] However, preparation of configurationally defined substituted allylboron reagents still remains a challenging task. The first part of this introduction will primarily focus on the syntheses of stable allylboronic esters, which have been widely used in carbonyl crotylations. Allylboronic esters are usually prepared by (1) addition of a stereodefined allylmetal to an electrophilic boronic ester; (2) addition of a vinylmetal reagent to an α-chloroboronic ester;[9] (3) one carbon homologation of a vinylboronic ester;[10] (4) metal catalyzed isomerization of vinylboronic ester;[11] (5) cross metathesis of a terminal olefin with vinylboronic ester;[12] (6) palladium catalyzed borylation of allyl electrophiles[13] (Figure 1.3).

---

[8] (a) Hall, D. G. Boronic Acid-based Receptors and Sensors for Saccharides. *In Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH:Weinheim, Germany, 2005; pp 441-475. (b) Yang, W.; Gao, X.; Wang, B. Biological and Medicinal Applications of Boronic Acids. In *Boronic Acids*; Hall, D. G., Ed.; Wiley-VCH:Weinheim, Germany, 2005; pp 481–512.

[9] (a) Wuts, P. G. M.; Thompson, A. P.; Callen, G. R. *J. Org. Chem.* **1983**, *48*, 5398. (b) Hoffman, R. W.; Schlapbach, A. *Tetrahedron* **1992**, *48,* 1959. (c) Hoffman, R. W.; Schlapbach, A. *Liebigs Ann. Chem.* **1990**, 1243.

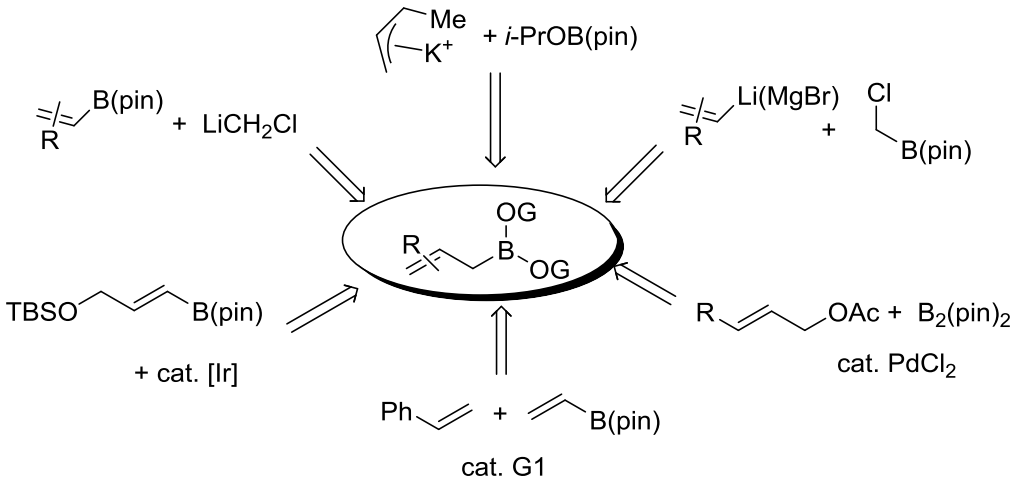
[10] Thadani, A, N.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 8051.

[11] Yamamoto, Y.; Miyaira, T.; Ohmura, T.; Miyaura, N. *J. Org. Chem*. **1999**, *64*, 296.

[12] (a) Yamamoto, Y.; Takahashi, M.; Miyaura, N. *Synlett* **2002**, 128. (b) Goldberg, S. D.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 807.

[13] (a) Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett*. **1996**, *37*, 6889. (b) Dutheuil, G.; Selander, N.; Szabo, K. J.; Aggarwal, V. K. *Synthesis* **2008**, *14*, 2293. (c) Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416.

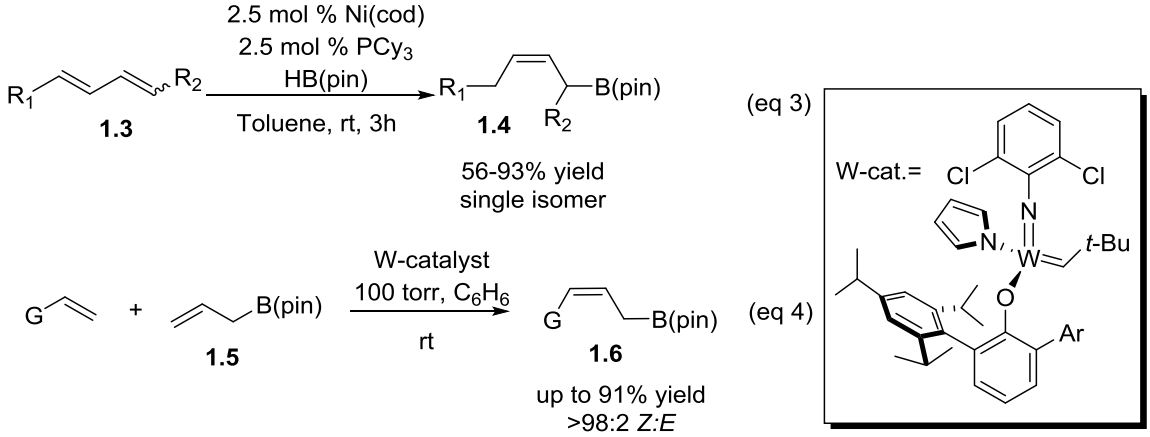
Figure 1.3. Syntheses of Crotylboron Reagents



The methods mentioned above are only (*E*)-selective or require the use of stoichiometric stereodefined (*Z*)-allylmetal reagents as starting material. A catalytic method to prepare (*Z*)-allylboronic esters would be valuable and attractive for the construction of *syn*-homoallylic alcohols (Scheme 1.3). This goal has been achieved by several research groups,[14] including the Morken group using a Ni-catalyzed 1,4-hydroboration of 1,3-dienes **1.3** (Scheme 1.4, equation 3)[15], and the Hoveyda group utilizing a W-based aryloxide pyrrolidine complex catalyzed (*Z*)-selective cross metathesis of allylboronic pinacol ester **1.5** with monosubstituted olefins (Scheme 1.4, equation 4).[16]

[14] For hydroboration of dienes, see: Satoh, M.; Nomoto, Y.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett*. **1989**, *30*, 3789.(b) Wu, J. Y.; Moreau, B.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 12915.
[15] (a) Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 2534. (b) Ely, R. J.; Morken, J. P. *Org. Synth*. **2011**, *88*, 342.
[16] Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J., Schrock, R. R.; Hoveyda. A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026.

Scheme 1.4. Selected Catalytic Routes to (*Z*)-Allylboronic Esters

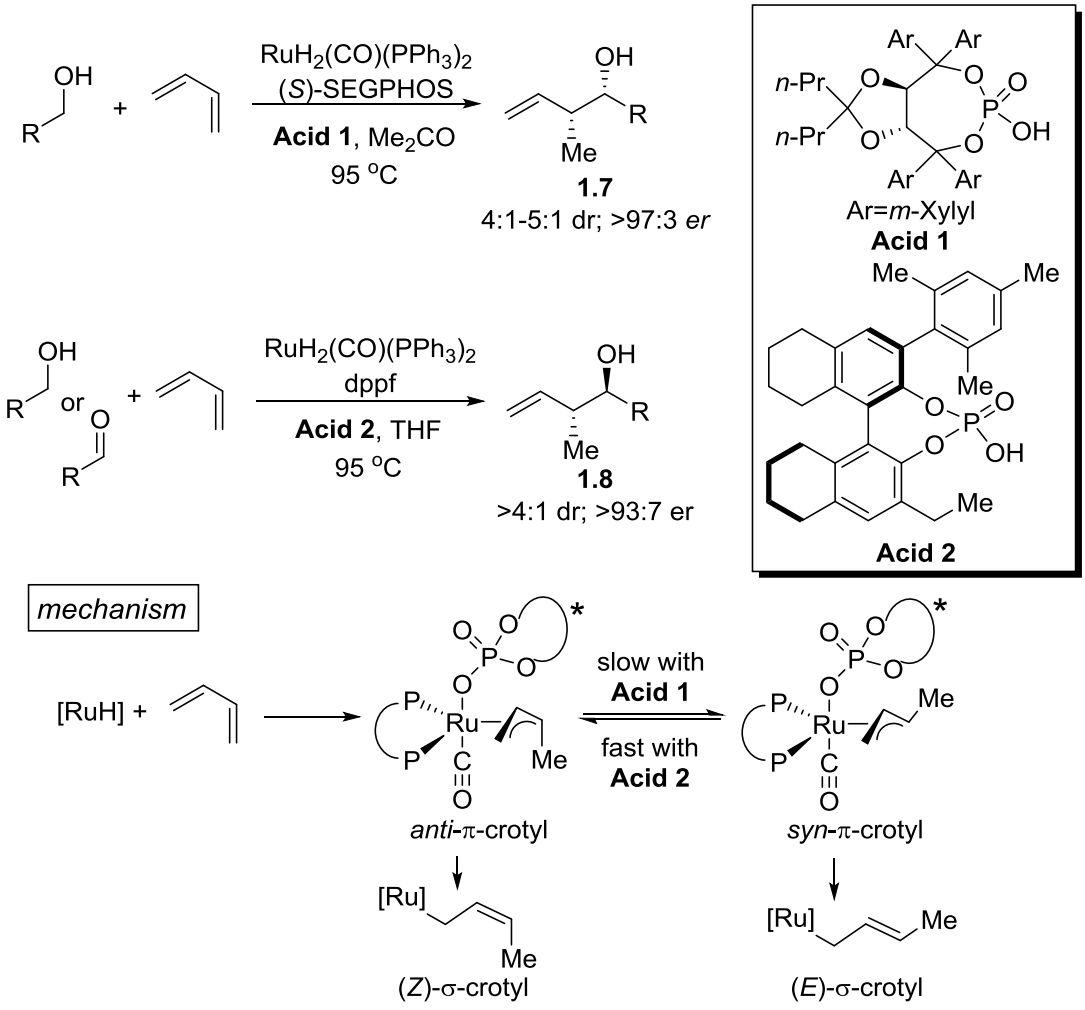


As described above, crotylboron reagents can be prepared selectively and add to carbonyls to provide homoallylic alcohols. Krishe and co-workers have developed an alternative method to construct polyketides *via* a Ru- and Ir-catalyzed enantio- and diastereoselective hydrohydroxylalkylation of butadiene and aldehyde.[17] This class of transfer hydrogenation reactions provides a powerful and novel way to construct ketide units that bypasses the use of stoichiometric chiral auxiliaries, premetallated carbon nucleophiles, and discrete alcohol-to-aldehyde redox reactions. Depending on the choice of catalytic chiral phosphoric acid, *syn*- or *anti*-products were obtained selectively in good diatereoselectivity and high enantioselectivity (Scheme 1.5). It is suspected that the *anti*-π-crotylruthinium intermediate is formed kinetically as a result of hydrometalation of the *s*-cis conformer of butadiene, and its isomerization is retarded in the presence of the

[17] For stereoselective ruthenium catalyzed crotylation of alcohol C–H bonds, see: (a) Zbieg, J. R.; Moran, J.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 10582; (b) Zbieg, J. R.; Yamaguchi, E.; McInturff, E. L.; Krische, M. J. *Science* **2012**, *336*, 324; (c) McInturff, E. L.; Yamaguchi, E.; Krische, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 20628. For iridium catalyzed allylation of alcohol C–H bonds, see: (d) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 6340; (e) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 14891; (f) Lu, Y.; Kim, I. S.; Hassan, A.; Del Valle, D. J.; Krische, M. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5018; (g) Hassan, A.; Lu, Y.; Krische, M. J. *Org. Lett*. **2009**, *11*, 3112; (h) Schmitt, D. C.; Dechert-Schmitt A.-M. R.; Krische, M. J. *Org. Lett*. **2012**, *14*, 6302; (i) Dechert-Schmitt, A.-M. R.; Schmitt, D. C.; Krische, M. J. *Angew. Chem. Int. Ed.***2013**, *52*, 3195.

sterically demanding TADDOL-derived phosphoric acid (**Acid 1**). Thus, the kinetic hydrometalation stereoselectivity is preserved as (*Z*)-σ-crotylruthenium intermediate and leads to the *syn*-diastereomer **1.7** after crotylation with an aldehyde.[17c] If the binol derived phosphoric acid (**Acid 2**) was used, *anti*-π-crotylruthenium intermediate will quickly isomerize to its *syn*-isomer, followed by crotylation with an aldehyde delivering *trans*-homoallylic alcohol **1.8**.[17b]

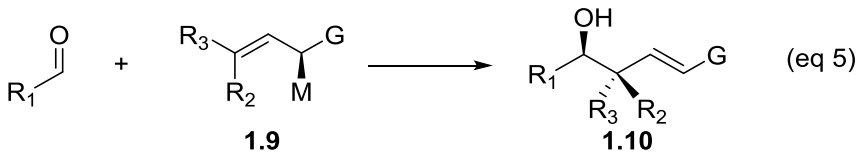
Scheme 1.5. Enantioselective Ruthenium-Catalyzed Crotylation *via* Butadiene Hydro-hydroxyalkylation



1.2.3. Crotylation with α-Chiral Crotyl Metals for Polyketide Syntheses

Aforementioned creative methods could rapidly construct ketide moieties, but the products only possess terminal olefins and require further functionalizations to construct internal olefins that are more commonly observed in polyketide natural products (Figure 1.1). However, such ketide fragment **1.10** with internal olefins can be prepared using chiral crotylation reagent **1.9** that contains other useful functional groups (Scheme 1.6, equation 5). Thus, methods to synthesize functionalized and enantiomerically enriched crotyl metal **1.9** are valuable for polyketide synthesis. These methods are generally divided into two categories: (1) those prepared from stoichiometric chiral auxiliary/ligand; (2) from achiral materials *via* asymmetric catalysis.

Scheme 1.6. General Asymmetric Crotylation of Aldehyde

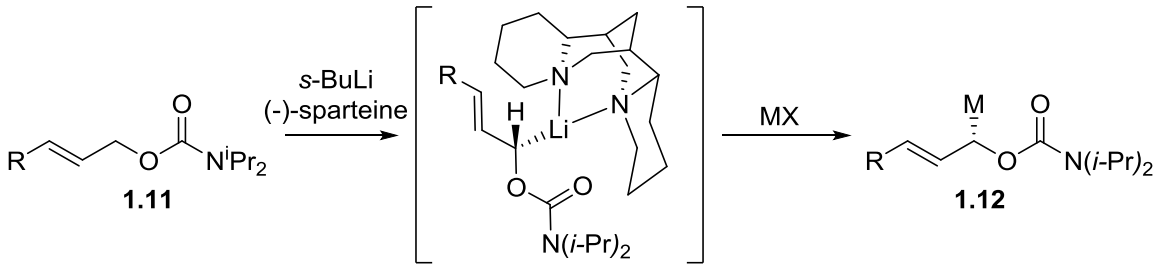


1.2.3.1. α-Chiral Crotylation Reagents Prepared Using Stoichiometric Auxiliary/Ligand

The enantioselective deprotonation of allylic carbamate **1.11**, followed by addition of an electrophilic metal halide, pioneered by Hoppe, is a powerful synthetic method to prepare α-chiral crotylation reagent **1.12** (Scheme 1.7).[18] Enantioselective deprotonation is usually achieved using an alkyl lithium as a base and a chiral diamine (e.g. sparteine) as a ligand; the most commonly used electrophilic metals are boron, silicon, titanium, and tin.[18b]

[18] For book and review, see: (a) Hoppe, D.; Christoph, G. Z.; Marek, I. (Eds.), *The Chemistry of Functional Groups Part 1*; Wiley: Chichester **2004**, 1055-1164. (b) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed*. **1997**, *36*, 2282.

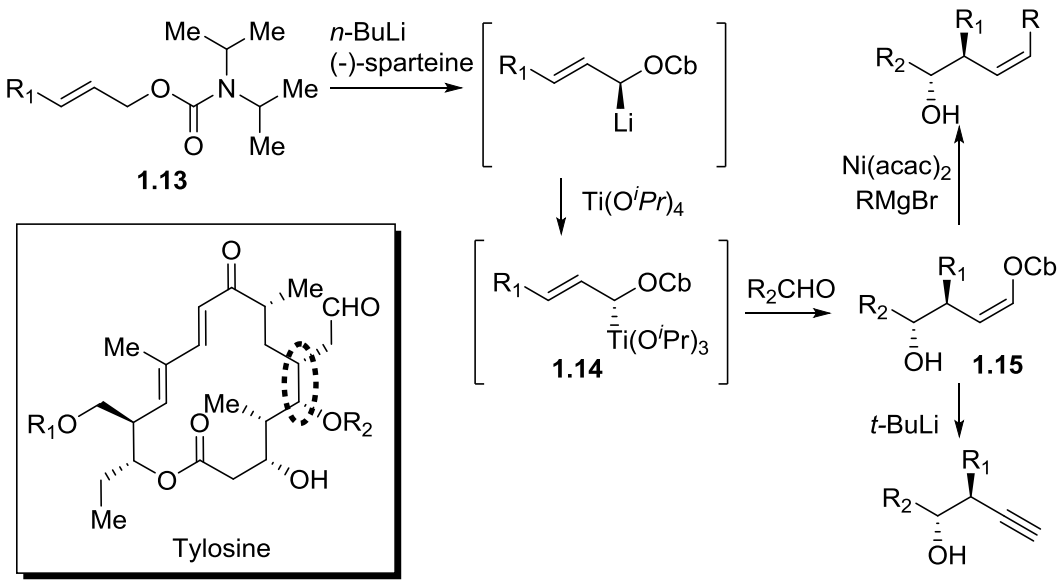
Scheme 1.7. (−)-Sparteine Mediated Enantioselective Deprotonation



Ardisson and co-workers have used this method to prepare chiral crotyltitanate **1.14** *via* sparteine-mediated deprotonation of allylic carbarmate **1.13** with *n*-BuLi; transmetalation to titanium *iso*-propoxide occurs with complete inversion of configuration (Scheme 1.8).[19] Chiral crotyltitanate **1.14** was treated with propionaldehyde, constructing (*Z*)-*anti*-homoallylic alcohol **1.15** with a versatile vinylcarbamate motif. Further transformations, including Fritsch-Buttenberg-Wiechell rearrangement [20] and nickel-catalyzed cross-couplings,[21] can convert vinylcarbamate **1.15** to key intermediates in the total synthesis of tyonolide [22] and discodermolide.[23] However, this method is limited to the synthesis of *anti*-adducts due to the stereochemical instability of crotyltitanate **1.14**.

[19] H. Paulsen. C. Graeve, D. Hoppe. *Synthesis* **1996,** 141.
[20] For a review, see: Knorr, R. *Chem. Rev*. **2004**, *104*, 3795.
[21] Kocienski, P.; Dixon, N. J. *Synlett*, **1989**, *1*, 52
[22] Berque, I.; Le Ménez, P. L.; Razon, P.; Mahuteau, J.; Férézou, J.-P.; Pancrazi, A.; Ardisson, J.; Brion, J.-D. *J. Org. Chem*. **1999**, *64*, 373.
[23] de Lemos, E.; Porée, F.-H.; Commerçon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Angew. Chem. Int. Ed*. **2007**, *46*, 1917.

Scheme 1.8. Chiral Crotyltitanate for the Synthesis of Homoallylic Alcohol

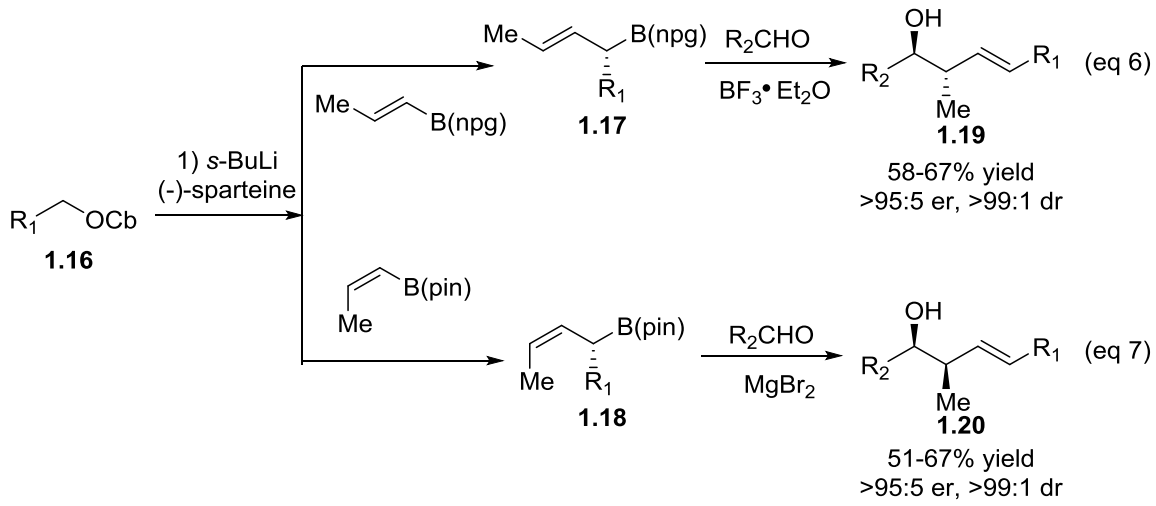


Very similar to Ardisson's strategy, Aggarwal and co-workers also took advantage of enantioselective deprotonation of allylic carbamates to prepare α-substituted allylboronic esters (Scheme 1.9). [24] Enantioselective deprotonation of carbamate **1.16** was achieved by sparteine ligated *s*-BuLi, followed by homologation with *trans*-crotylboronic ester, delivering chiral crotyl boronic esters **1.17** (Scheme 1.9, equation 6). Upon addition of an aldehyde, *anti*-homoallylic alcohols **1.19** were produced *via* allylboration with excellent diastereoselectivity and chirality transfer. When *cis*-crotylboronic ester **1.18** was used, *syn*-adducts **1.20** were obtained (Scheme 1.9, equation 7). Unlike crotyltitanate, both *syn*- and *anti*-adducts are accessible due to the stable stereochemical geometry of crotylboronic esters (**1.17** and **1.18**). In both cases, Lewis acids were necessary to accelerate allylboration.[25]

[24] (a) Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2010**, *132*, 4025. (b) Chen, L. Y.; Scott, H. K.; Hesse, M. J.; Willis, C. L.; Aggarwal. V. K. *J. Am. Chem. Soc.* 2013, *135*, 5316.

[25] (a) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc*. **2003**, *125*, 10160. (b) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem. Int. Ed*. **2003**, *42*, 4732. (c) Rauniyar, V.; Hall, D. G.

Scheme 1.9. Production and Allylation of α-Substituted *E*- and *Z*-Crotyl Boronic Esters



Chiral 1,1-dimetal crotyl reagents would furnish allylation products with vinylmetal groups for further functionalization as demonstrated by Roush (Scheme 1.10).[26] The enantiomerically enriched 1,1-dimetal crotyl reagent **1.22** was prepared by an enantioconvergent hydroboration of racemic allenylstannane **1.21** with Brown's *d*-diisopinocampheyl-borane ((*d*Ipc)$_2$BH).[27] Hydroboration of one enantiomer of **1.21** directly provides desired **1.22**, while the hydroboration product of the other enantiomer is unstable and isomerizes to **1.22** *via* 1,3-boratropic shift.[28] Crotylboron **1.22** reacted with an aldehyde to provide *anti*-homoallylic alcohol **1.23** with good yield and excellent

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J. Am. Chem. Soc. **2004**, *126*, 4518. (d) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett.* **2000**, *2*, 1217.

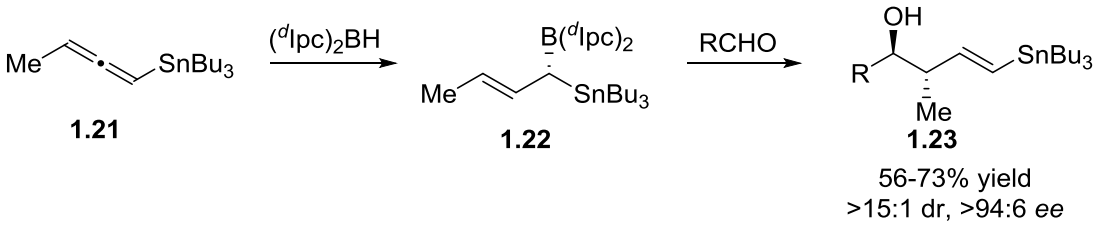
[26] Chen, M.; Roush, W. R. *J. Am. Chem. Soc*. **2011**, *133*, 5744.

[27] (a) Brown, H. C.; Yoon, N. M. *Isr. J. Chem*. **1977**, *15*, 12. (b) Brown, H. C.; Singaram, B. *J. Org. Chem.* **1984**, *49*, 945.

[28]) (a) Hancock, K. G.; Kramer, J. D. *J. Am. Chem. Soc*. **1973**, *95*, 6463. (b) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem*. **1977**, *132*, 9. (c) Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem*. **1981**, *46*, 1309. (d) Henriksen, U.; Snyder, J. P.; Halgren, T. A. *J. Org. Chem*. **1981**, *46*, 3767. (e) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc*. **1985**, *107*, 2564. (f) Wang, K. K.; Gu, Y. G.; Liu, C. *J. Am. Chem. Soc*. **1990**, *112*, 4424. (g) Gu, Y. G.; Wang, K. K. *Tetrahedron Lett*. **1991**, *32*, 3029. (h) Narla, G.; Brown, H. C. *Tetrahedron Lett*. **1997**, *38*, 219. (i) Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 359. (j) Canales, E.; Gonzalez, A. Z.; Soderquist, J. A. *Angew. Chem. Int. Ed*. **2007**, *46*, 397. (k) Gonzalez, A. Z.; Soderquist, J. A. *Org. Lett*. **2007**, *9*, 1081.

diastereoselectivity. The product contains vinylstannane as a functional group which can be used in Stille cross coupling reactions.

Scheme 1.10. Production and Allylation of Chiral α-Stannane Crotylboron Reagent



1.2.3.2. Chiral Crotyl Metals Prepared from Achiral Materials *via* Asymmetric Catalysis

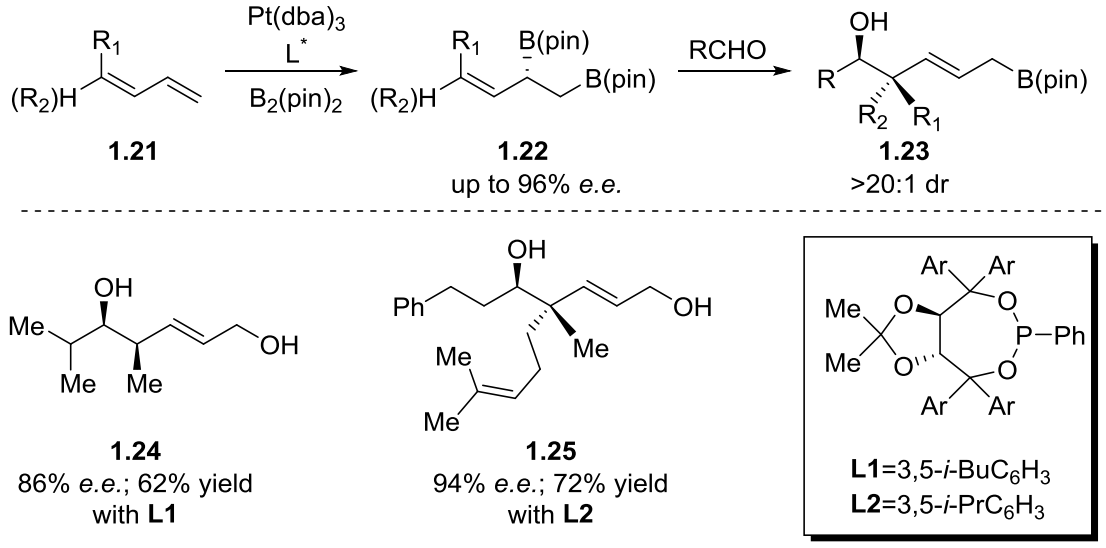
Above mentioned reactions can efficiently generate α-chiral crotyl metal reagents and deliver both *syn*- and *anti*-vinylogous aldol products; however, all of these reactions involve the use of stoichiometric chiral reagents [e.g. (−)-sparteine and (+)-pinene], and stoichiometric amount of base and metal (e.g. BuLi and tin). Such auxiliary based chemistry is not desired from the standpoint of atom-economy when compared to catalytic methods.[29] Thus, it is extremely valuable to synthesize enantiomerically enriched α-chiral crotyl metal reagents from achiral and readily available hydrocarbon feedstocks *via* an asymmetric catalytic method.

Morken and co-workers have disclosed an asymmetric Pt-catalyzed 1,2-diboration of achiral *cis*- and 1,1-disubstituted 1,3-dienes **1.21** delivering chiral crotylboronic pinacol ester **1.22** with good enantioselectivity (Scheme 1.11).[30] These 1,2-diboron intermediates participated in allylation reactions with various aldehydes furnishing *syn*-homoallylic alcohols **1.23** with good distereoselectivity and chirality transfer. The

[29] Trost, B. M. *Angew. Chem. Int. Ed*. **1995**, *34*, 259.
[30] Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem. Int. Ed*. **2012**, *51*, 521.

allylboronic ester in product **1.23** could serve as a functional handle for further transformations, such as direct oxidation to allylic alcohols (Scheme 1.11, **1.24** and **1.25**) and tandem allylations in the presence of a second carbonyl (Scheme 1.12). Only *syn*-homoallylic alcohols can be prepared by this method due to the fact that Pt-catalyzed 1,2-diboration only occurs on *cis*- and 1,1-disubstituted 1,3-diene substrates.

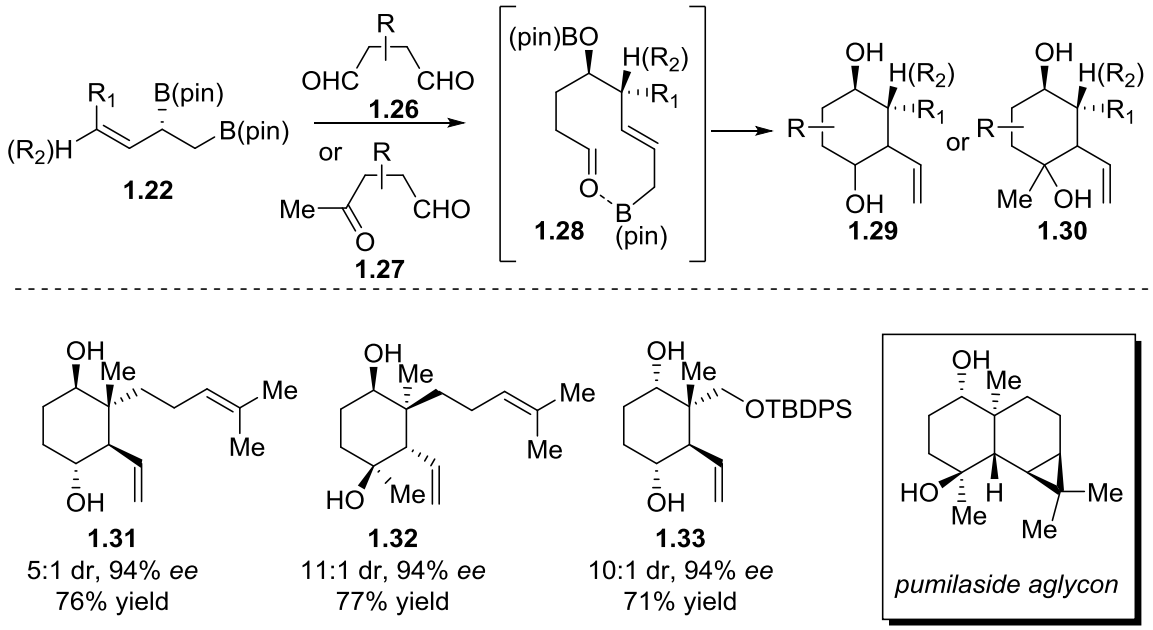
Scheme 1.11. Catalytic Diene 1,2-Diboration to Produce α-Chiral Crotylboron Reagent



When diboron **1.22** was treated with dialdehyde **1.26** or ketoaldehyde **1.27**, the remaining allylboronic ester in **1.23** reacted intramolecularly with the second carbonyl to build up carbocyclic structures (**1.31-1.33**) with high diastereo- and enantioselectivity (Scheme 1.12).[31] This methodology rapidly constructed the core structure of pumilaside aglycon and the synthesis was completed in only six steps from simple achiral hydrocarbons.

[31] Ferris, G. E.; Hong, K.; Roundtree, I. A.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 2501.

Scheme 1.12. Tandem Diene Diboration/Double Allylation of Dicarbonyls

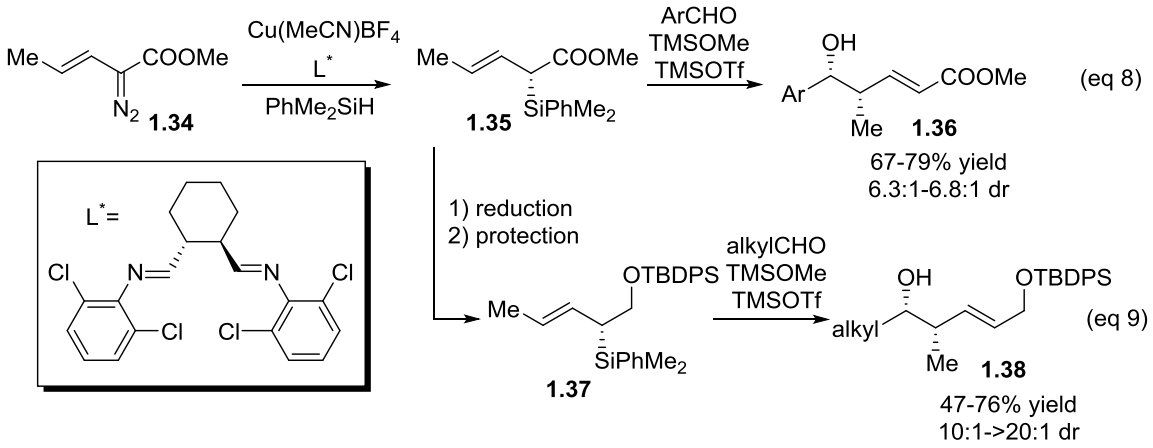


Besides α-chiral crotylboron reagents (Scheme 1.9, 1.10 and 1.11), α-chiral crotyl silanes also play an important role in polyketide fragment syntheses.[32] It is worth pointing out that, unlike crotylboron reagents, crotylsilanes often react with carbonyls under an "open transition state" mechanism.[33] Using methods developed by Panek and co-workers, optically active crotylsilane **1.35** was synthesized *via* Cu(I)-catalyzed enantioselective Si-H insertion of an α-diazo vinylester **1.34** (Scheme 1.13).[34]After recrystallization from pentane to obtain high enantiomeric excess, crotylsilane **1.35** underwent Lewis acid mediated crotylation with aromatic aldehydes generating vinylogous aldol adducts **1.36** in good yield and diatereoselectivity (Scheme 1.13, equation 8). In order to obtain synthetically useful levels of yield for aliphatic aldehydes, it was necessary to use

[32] (a) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, 95, 1293. (b) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, 113, 9868. (c) Panek, J. S.; Yang, M.; Xu, F. *J. Org. Chem.* **1992**, 57, 5790.
[33] Fleming, I. *Org. React.* **1989**, *37*, 57.
[34] Wu, J.; Chen, Y.; Panek, J. S. *Org. Lett*. **2010**, *12*, 2112.

crotylsilane **1.37** which is prepared by a two-step reduction/protection sequence from **1.35** (Scheme 1.13, equation 9).

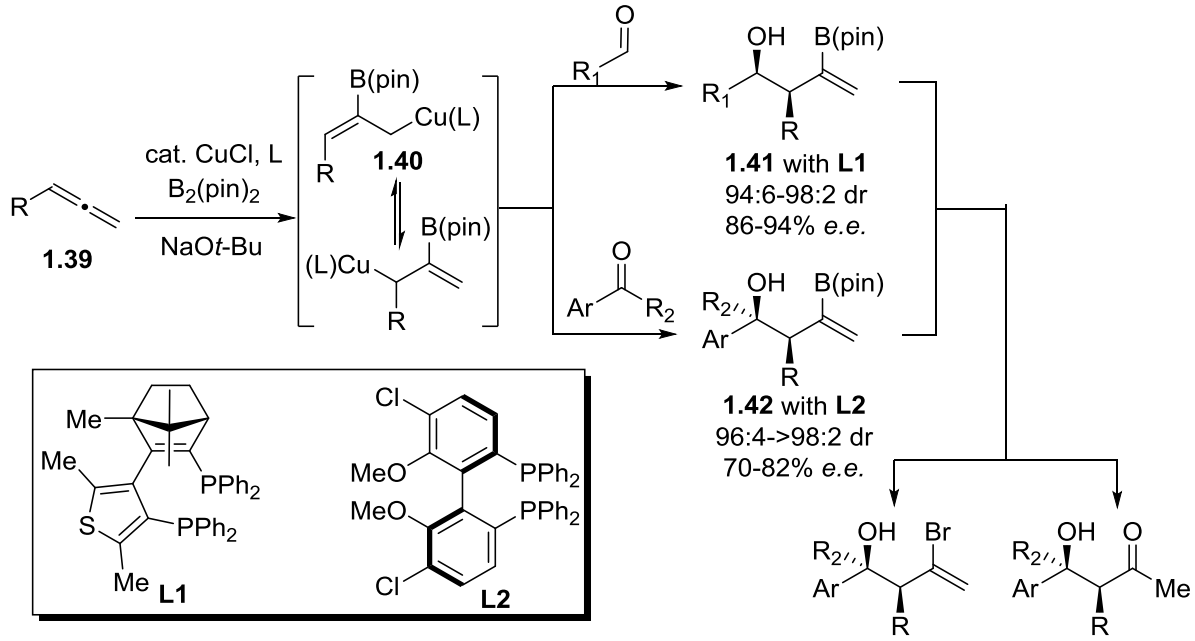
Scheme 1.13. Production and Crotylation of Enantiomerically Enriched Crotyl Silanes



Most of the aforementioned chiral crotylboronates and crotylsilanes are reasonably stable for purification (e.g. crotylsilane **1.35**); however, it would be more efficient and operationally simple if such α-chiral crotylmetal reagents were generated and used *in-situ*. Recently, Hoveyda and co-workers reported the generation of chiral allylcopper reagent **1.40** from copper boration of achiral mono-substituted allene **1.39**, followed by an *in-situ* addition to aldehydes and ketones (Scheme 1.14).[35] The stereoselectiviety was controlled by a chiral bulky phosphine (**L1** and **L2**) that ligated to copper. *Syn*-homoallylic alcohols **1.41** and tertiary alcohols **1.42** were obtained with high diastereoselectivity and moderate to good enantioselectivity. Most importantly, these products (**1.41** and **1.42**) contain a valuable vinylboron moiety for further functionalization, such as oxidation to form methyl ketones, C-B bond bromination to produce vinyl bromides, and Suzuki cross couplings.

[35] Meng, F.-K.; Jang, H.-J.; Jung, B.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 5046.

Scheme 1.14. Production of Chiral Crotylcopper and *in situ* Addition to Aldehydes and Ketones

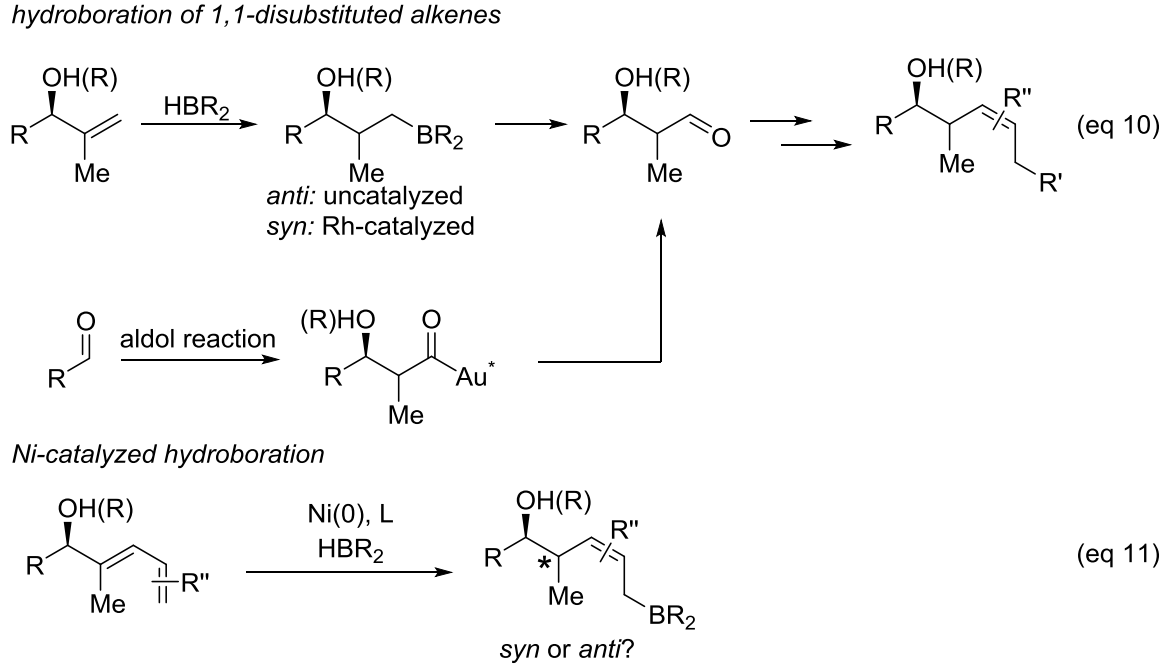


Great success has been achieved in the preparation of α-chiral crotyl metal reagents followed by their allylation to carbonyls. However, excluding Ardisson's example (Scheme 1.8), these methodologies only provide homoallylic alcohols with *trans*-alkenes or 1,1-disubstituted alkenes. But a number of polyketides (Figure 1.1) contain *cis*-alkenes bearing adjacent propionate moieties, which were usually prepared by *cis*-selective olefination reactions of aldehydes[36] prepared from hydroboration of 1,1-disubstituted alkenes (Scheme 1.15, equation 10). The main drawback of this strategy is that multiple transformations are required to construct appropriate olefin reagents. Based on previously published results[15] in our laboratory, it was considered that a Ni-catalyzed diastereoselective 1,4-hydroboration of a chiral dienol would deliver the required ketide

[36] (a) Kishi, Y. *Aldrichimica Acta.* **1980**, *13,* 23. (b) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981***, 37, 3873.* (c) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (d) Midland, M. M.; Kwon, Y. C. *J. Am. Chem. Soc.* **1983**, *105*, 3725. (e) Houk, K. N.; Rondan, N. G.; Wu, Y.-D.; Netz, J. T.; Paddon-Row: M. N. *Tetrahedron* **1984**, *40*, 2257.

unit containing both propionate moiety and adjacent *cis*-alkene (Scheme 1.15, equation 11). We expected the neighboring alcohol/ether functional groups may control the diastereoselectivity and allow formation of the *syn*- or *anti*-product.

Scheme 1.15. Ketide Sythesis *via* Ni-catalyzed Diastereoselective Hydroboration



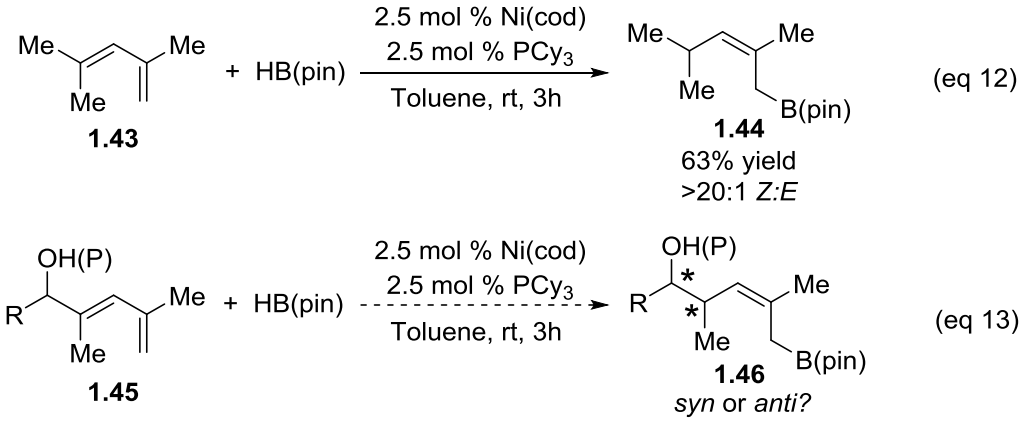
1.3. Development of Ni-Catalyzed Diastereoselective 1,4-Hydroboration of 1,3-Dienols[37]

Previously, our laboratory has reported a Ni-catalyzed hydroboration of 1,3-dienes providing *cis*-allylboronic ester with high yield and *Z*-selectivity.[15] Hydroboration of 2,4-dimethyl-pentadiene **1.43** resulted a trisubstituted allylboronic ester **1.44** with high *Z*-selectivity and yield (Scheme 1.16, equation 12). This example is quite interesting and important because (1) hydroboration of trisubstituted olefin is rare;[38] (2) synthetically

[37] Ely, R. J.; Yu, Z.; Morken, J. P. manuscript in preparation.
[38] (a) Smith, S. M.; Takacs, J. M. *J. Am. Chem. Soc*. **2010**, *132*, 1740. (b) Smith, S. M.; Thacker, M. C.;Takacs, J. M. *J. Am. Chem. Soc*. **2008**, *130*, 3734. (c) Hadebe, S. W.; Robinson, R. S.

challenging trisubstitued *Z*-olefin is prepared in one catalytic step. Thus, further investigation of this class of substrates was warranted. It is worth noting that a chiral center is built during this process if the starting material is prochiral; thus it provided an opportunity to study the diastereoselectivity of hydroboration of corresponding chiral 1,3-dienes **1.45** bearing an adjacent hydroxyl group (Scheme 1.16, equation 13).

Scheme 1.16. Design of Ni-catalyzed 1,4-Hydroboration of Chiral 1,3-Dienes



The TBS-protected dienol ether **1.47** was chosen as a probe substrate to test our hypothesis. Diene **1.47** was subject to standard hydroboration conditions (2.5 mol % $Ni(cod)_2$, 2.5 mol % PCy_3, 0.25 M in toluene), and we were pleased to isolate the *syn*-allylic alcohol **1.48** with 10:1 dr and 86% yield after oxidation (Table 1.1, entry 1). Several ligands were screened, but none of them were as effective as tricyclohexyl-phosphine (Table 1.1, entry 2 and 3). Changing the solvent to THF enhanced diastereoselectivity (Table 1.1, entry 4; 12:1 vs 10:1); as did lowering the temperature to 0 ^{o}C (Table 1.1, entry 5; 14:1 vs 12:1). Further decreasing temperature to −20 ^{o}C caused incomplete conversion even after prolonged reaction time (Table 1.1, entry 6).

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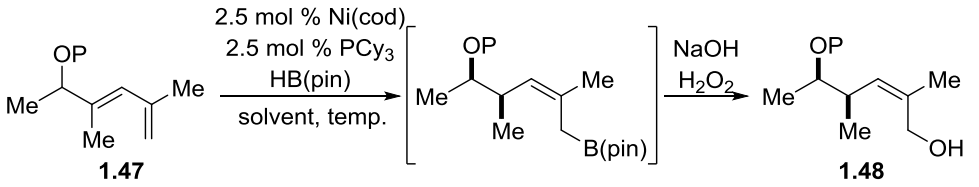
*Tetrahedron Lett.***2006**, *47*, 1299. (d) Edwards, D. R.; Crudden, C. M.; Yam, K. *Adv. Synth. Catal.* **2005**, *347*, 50. (e) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671. (f) Evans, D. A.; Fu, G. C.; Anderson, B. A. *J. Am. Chem. Soc*. **1992**, *114*, 6679.

Considering the alcohol protecting group could dramatically affect reaction selectivity,[39] various protecting groups with different sizes and electronic properties were tested. A smaller TES protecting group on the alcohol led to good yield but slightly lower diastereoselectivity compared to the TBS-protected substrate (Table 1.1, entry 7). The larger TBDPS-protecting group produced the desired product as a single diastereomer (determined by ^{1}H-NMR), but it required longer reaction time at elevated temperature in order to reach full conversion (Table 1.1, entry 8). Both the benzyl protecting group and the free alcohol diminished diastereoselectivity and isolated yield (Table 1.1, entry 9 and 10). It's worth pointing out that 1,4-hydroboration products were the only detectable regioisomer in all examples.

[39] (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1988**, *110*, 6917. (b) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1991**, *114*, 6671. (c) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc*. **1983**, *105*, 2487.

Table 1.1. Reaction Condition Optimization and Protecting Group Evaluation[a]



1.47 **1.48**

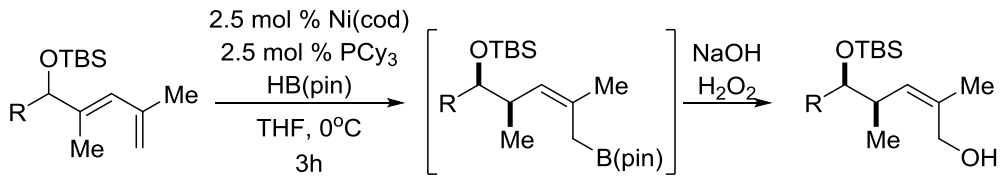
entry	P	solvent	temp. (^{o}C)	dr[b]	yield(%)[c]
1	TBS	toluene	rt	10:1	86
2[d]	TBS	toluene	rt	6:1	82
3[e]	TBS	toluene	rt	2:1	82
4	TBS	THF	rt	12:1	86
5	TBS	THF	0	14:1	89
6[f]	TBS	THF	-20	14:1	N.D.
7	TES	THF	0	12:1	93
8[g]	TBDPS	THF	rt	>20:1	80
9[f]	Bn	THF	0	7:1	72
10[h]	H	THF	0	6:1	56

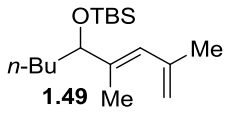
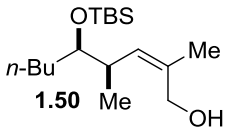
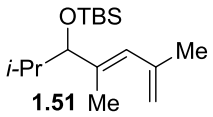
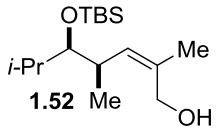
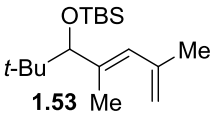
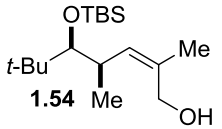
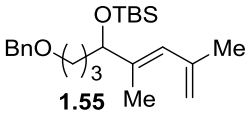
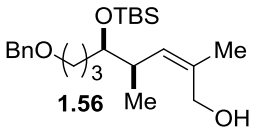
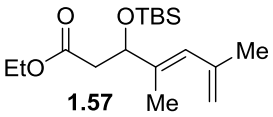
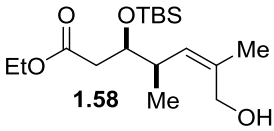
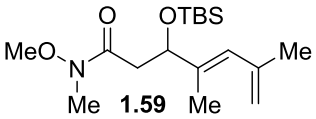
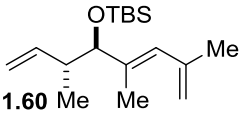
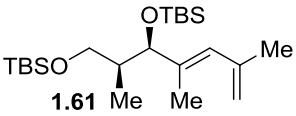
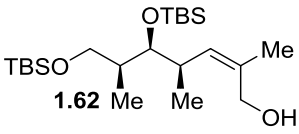
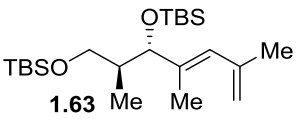
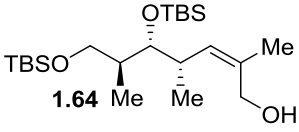
[a] Reactions were conducted at a concentration of 0.25 M and oxidized with 30% H_2O_2 and 3M NaOH. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield of purified material. Values are an average of two experiments. [d] Reaction run with P(Cyp)$_3$ as ligand. [e] Reaction run with P(*n*-Bu)$_3$ as ligand. [f] Reaction run for 12 h. [g] Reaction run for 24 h. [h] 2.0 equiv. HB(pin) employed.

With optimum reaction conditions in hand (2.5 mol % Ni(cod)$_2$, 2.5 mol % PCy$_3$, 0.25M in THF, 0 ^{o}C), various TBS-protected dienols were tested in Ni-catalyzed hydroboration reactions (Table 1.2). Linear alkyl substitution at the carbinol position (**1.49**) (Table 1.2, entry 1) enhanced diastereoselectivity while maintaining good yield compared to methyl substituted dienol ether **1.39** (Table 1.1). Sterically demanding substrates (**1.51** and **1.53**) also participated in this reaction delivering desired product, though longer reaction time and elevated temperature were required for full conversion (Table 1.2, entry 2 and 3). Substrates bearing ether (**1.55**) and ester (**1.57**) functional

groups were well tolerated in this reaction and provided desired allyl alcohols with high levels of diastereoselectivity (Table 1.2, entry 4 and 5). Unfortunately, Weinreb's amide (**1.59**) and terminal olefin (**1.60**) were not tolerated in nickel-catalyzed hydroboration (Table 1.2, entry 6-7). These reactions might be inhibited by strong intramolecular coordination of basic functional groups to the metal center, preventing migratory insertion. Enantiomerically enriched dienol ether **1.61** provided the *syn/syn*-stereotriad **1.62** with good yield and diastereoselectivity (Table 1.2, entry 8), while *anti/syn*-stereotriad **1.64** was obtained from the *anti*-substrate **1.63** (Table 1.2, entry 9).

Table 1.2. Substrate Scope of Ni-catalyzed Hydroboration[a]



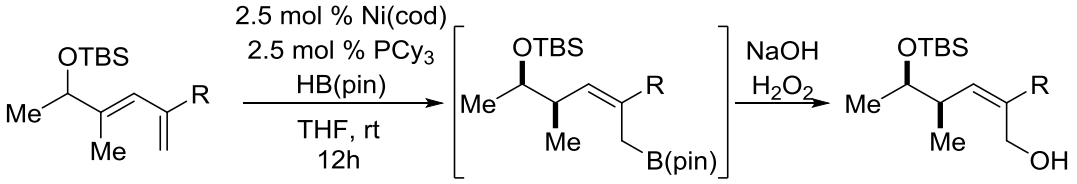
entry	substrate	product	yield (%)[b]	dr
1	 **1.49**	 **1.50**	90	>20:1
2[c]	 **1.51**	 **1.52**	98	10:1
3[c,d]	 **1.53**	 **1.54**	86	6:1
4	 **1.55**	 **1.56**	88	>20:1
5[e]	 **1.57**	 **1.58**	80	>20:1
6	 **1.59**	-	-	-
7[c,f]	 **1.60**	-	-	-
8[c]	 **1.61**	 **1.62**	91	6:1
9[c]	 **1.63**	 **1.64**	77	6:1

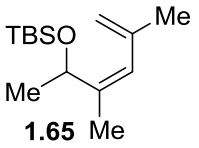
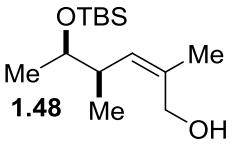
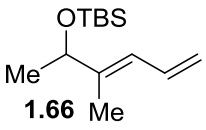
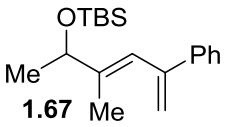
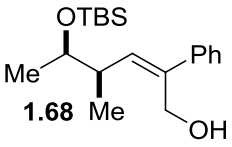
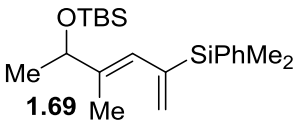
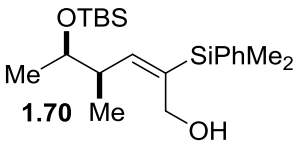
[a] Reactions conducted at [substrate] = 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Isolated yield of purified material. Values are an average of two experiments. [c] Reaction run for 12 h. [d] Reaction run at rt. [e] Oxidation with buffered (pH = 7) 30% H_2O_2. [f] Reaction run at 40 °C.

Substrates with functionalized dienes were also tested (Table 1.3). A mixture of 3:1 *E*:*Z*-dienes **1.65** participated in this catalytic hydroboration reaction, although higher temperature was required for complete conversion (Table 1.3, entry 1). Interestingly, both (*E*)- and (*Z*)-isomers gave the same *syn*-diastereomer **1.48**, suggesting that it's not necessary to prepare isomerically pure 1,3-diene for this hydroboration methodology. Considering the *s*-cis conformer of diene is the active species, it is not surprising that diminished reactivity was observed when 2-methyl substitution was removed (Table 1.3, entry 2). This is because the 2-methyl group of **1.47** off-sets the A(1,3) strain introduced by converting *s*-trans conformer to *s*-cis conformer (Scheme 1.17, equation 14). Thus, extra energy was required to achieve the reactive *s*-cis conformer in the absence of 2-methyl substitution in **1.66** (Scheme 1.17, equation 15). The required substitution at 2-position was not limited to methyl group; both phenyl- (**1.67**) and $PhMe_2Si$-substituted (**1.69**) dienes participated in the hydroboration process to construct trisubstituted (*Z*)-olefin with good yield and high diastereoselectivity (Table 1.3, entry 3 and 4). It is worth pointing out that the vinylsilane moiety in **1.70** could serve as a handle for further functionalization. [40] Thus, various trisubstituted (*Z*)-olefins bearing different vinylsubstitutions can be prepared *via* this intermediate vinylsilane.

[40] For selected vinylsilane transformations: (a) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (b) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1375. (c) Hiyama, T. in: *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: Negishi, E-i.), Wiley-Interscience, New York, **2002**, Vol. 1, 285–309; (d) Hiyama, T. in: *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: Diederich, F.; Stang, J. P.), Wiley-VCH, Weinheim, **1998**, pp. 421–452. (e) Colvin, E. W. *Silicon in Organic Sythesis.*, Butterworths, **1981**. (f) Pawluc, P.; Prukała, W.; Marciniec, B. *Eur. J. Org. Chem.* **2010**, 219. (g) Trost, B.M.; Ball, Z. T.; Laemmerhold, K. M. *J. Am. Chem. Soc.*, **2005**, *127*, 10028. (i) Sore, H. F; Galloway, W. R. J. D.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 1845.

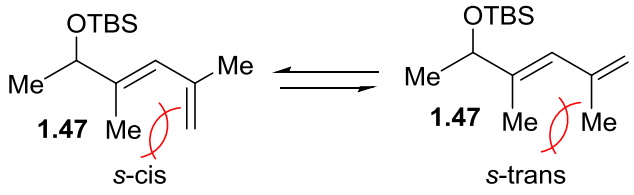
Table 1.3. Substrates with Non-methyl Substituted Dienes[a]

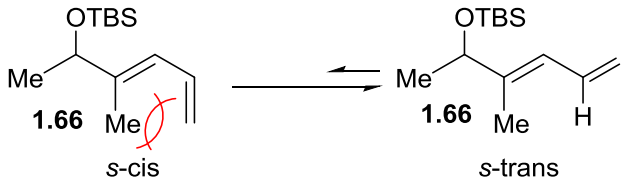


entry	substrate	product	yield (%)[b]	dr
1[c]	 **1.65**	 **1.48**	40	17:1
2	 **1.66**	-	-	-
3[d]	 **1.67**	 **1.68**	91	9:1
4[e]	 **1.69**	 **1.70**	84	>10:1

[a] Reactions conducted at [substrate] = 0.25 M and oxidized with 30% H_2O_2 and 3 M NaOH. [b] Isolated yield of purified material. Values are an average of two experiments. [c] 3:1 (*Z*:*E*)-mixture. [d] Reaction run at 60 °C. [e] Reaction run at 40 °C.

Scheme 1.17. Explanation of the Importance of 2-Methyl Substitution





Allylboronates are versatile intermediates;[41] however, in the examples above they were only oxidized to allylic alcohols (Table 1.1, 1.2 and 1.3). Thus, other useful transformations were carried out on the intermediate allylboronic esters **1.71** from Ni-catalyzed hydroboration (Scheme 1.18). For example, one carbon homologation[42] was performed to construct homoallylic alcohol **1.72** with excellent yield and without erosion of diastereoselectivity. With Aggarwal's selective protodeboration procedure,[43] 1,1-disubstituted alkene **1.73** could be isolated with good yield and regioselectivity. Using *m*CPBA, the trisubstituted alkene of allylboronic ester **1.71** was epoxidized with concomitant oxidation of the C-B bond furnishing epoxide **1.74** with good diastereoselectivity. The observed *syn*-selectivity of **1.74** was likely the result of approach of *m*CPBA from the least hindered face of the olefin, while minimizing A(1,3) strain.[44] It is necessary to point out that the intermediate allylboronic ester **1.71** was used directly after Ni-catalyzed hydroboration without any purification in all of these transformations.

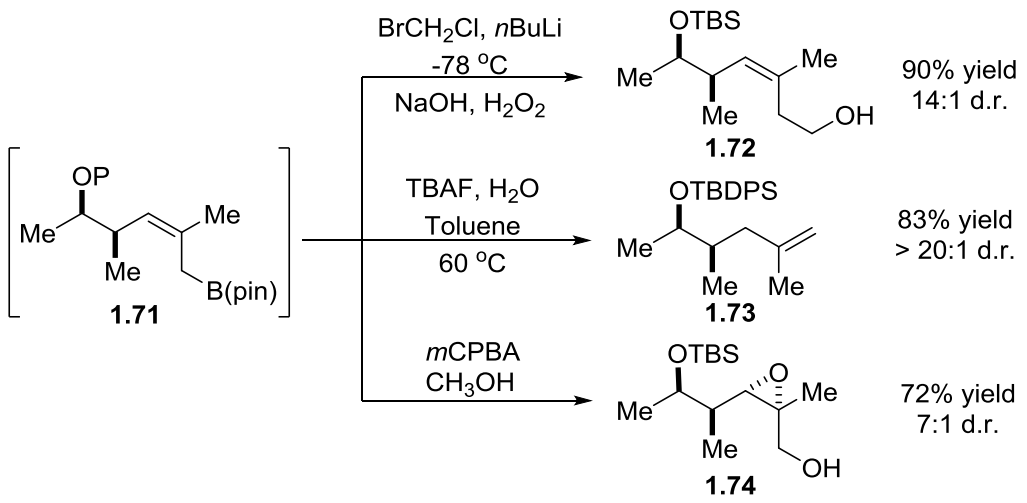
[41] For a review of Suzuki-Miyaura coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. For halogenations, see: (b) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456. For examples and review of 1,2-migration, see: (c) Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem. Eur. J*. **2000**, *6*, 1840. (d) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chemical Record* **2009**, *9*, 24. (e) Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**,*134,* 16449. *(f)* Bagutski, V.; Elford, T. G.; Aggarwal, V. K. *Angew. Chem. Int., Ed*. **2011**, *50*, 1080.

[42] (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (b) Chen, A. C.; Ren, L.; Crudden, C. M. *Chem. Commun.* **1999**, 611. (c) Chen, A. C.; Ren, L.; Crudden, C. M. *J. Org. Chem.* **1999**, *64*, 9704. (d) Ren, L.; Crudden, C. M. *Chem. Commun.* **2000**, 721.

[43] Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096.

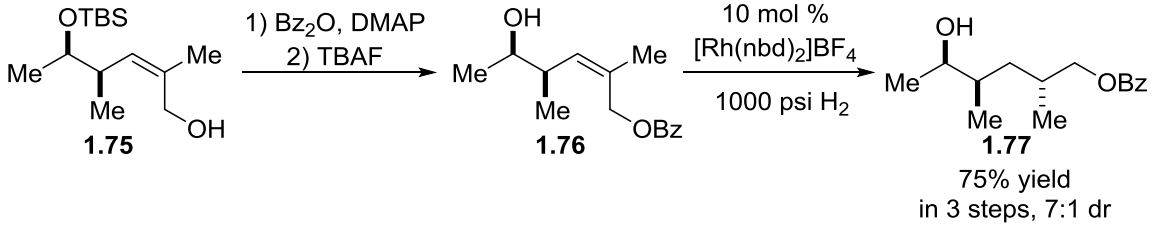
[44] Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc*. **1997**, *119*, 12150.

Scheme 1.18. Transformations of Intermediate Allylboronic Pinacol Ester



Directed catalytic hydrogenation of trisubstituted olefin **1.76**, which was prepared *via* two-step sequence from hydroboration product **1.75**, gave fully saturated compound **1.77** with good yield and diastereoselectivity (Scheme 1.19). The skipped methyl and adjacent *syn*-propionate moiety within **1.77** map onto common polyketide framework. This demonstrated that Ni-catalyzed hydroboration of chiral dienol is also capable of delivering saturated polyketide backbones.

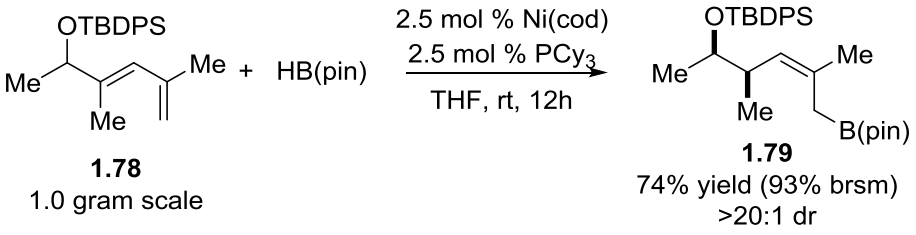
Scheme 1.19. Directed Catalytic Hydrogenation of Hydroboration Product



To examine the synthetic utility of Ni-catalyzed diastereoselective hydroboration, a gram scale reaction was performed (Scheme 1.20). The easily accessible TBDPS-protected dienol ether **1.78** was subject to standard hydroboration conditions. Although the reaction didn't reach full conversion after prolonged reaction time (which may be attributed to degradation of active catalyst over time), the desired allylboronic ester **1.79**

was easily separated from the unreacted starting material with excellent diastereo-selectivity and good yield based on recovered starting material.

Scheme 1.20. Gram Scale of Ni-Catalyzed Hydroboration



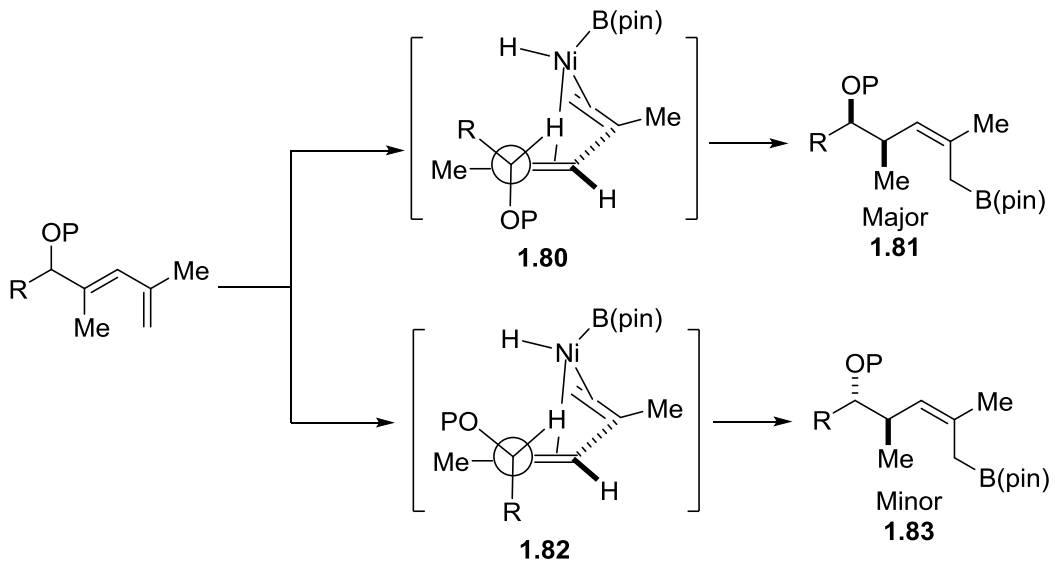
1.78
1.0 gram scale

1.79
74% yield (93% brsm)
>20:1 dr

The excellent diastereoselectivity in the above hydroboration examples can be explained by transition states shown in Figure 1.4, similar to a hypothesis made by Burgess.[45] We hypothesize that the nickel complex approaches the diene in a manner that the C-O bond, the best π-acceptor at the carbon stereocenter, is *anti*-planar to the incoming metal complex (**1.80**). This would allow maximized stabilization of the newly formed bond by lowering the HOMO-LUMO energy gap due to the mixing of π* of the diene and σ* of the C-O bond. At the same time, in order to minimize steric interaction, hydrogen (the smallest group at the carbon stereocenter) is preferentially directed towards the large metal center. Thus, the desired *syn*-diastereomer **1.81** is produced *via* transition state **1.80**. This model also explains the observed trend that larger protecting groups enhance diastereoselectivity due to the increased undesired interaction in undesired transition state **1.82**.

[45] Burgess, K.; van der Donk, W. A.; Jarstifer, M. B.; Ohlmeyer, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 6139.

Figure 1.4. Proposed Model for Ni-Catalyzed Hydroboration



1.4. Conclusion and Outlook

We have developed a Ni-catalyzed 1,4-hydroboration of chiral 1,3-dienols that efficiently constructs polyketide fragments with *syn*-propionate moieties bearing adjacent challenging (*Z*)-trisubstituted olefins. A wide range of substituents were tolerated and the intermediate allylboronic ester was successfully transformed to various functional groups. This methodology is developed as a tool to construct challenging structures and facilitate polyketide natural product synthesis. It is of great interest to apply this method to complex molecule syntheses, such as (+)-discodermolide (Figure 1.1) whose C9-C15 fragment maps on closely to the hydroboration product (Chapter 2).

1.5. Experimental Procedures

General Information

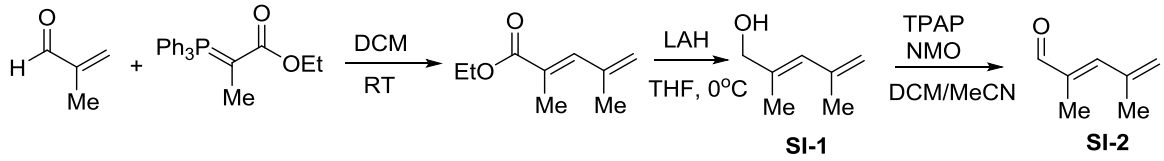
^{1}H-NMR spectra were recorded on Varian Unity Inova 500 MHz and Varian Gemini 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm, C_6D_6: 7.16 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), coupling constants (Hz) and assignment. $^{13}C\{^{1}H\}$NMR spectra were recorded on Varian Unity Inova 500 MHz (125 MHz) and Varian Gemini 400 MHz (100 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.23 ppm). Infrared (IR) spectra were recorded on a Bruker Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (ESI) was performed at Boston College, Chestnut Hill, MA. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Chromatograph equipped with an auto sampler and a Waters photodiode array detector with isopropanol as the modifier.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 40-63 μm) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid (PMA) in ethanol, potassium permanganate ($KMnO_4$) in water, or cerium (IV) sulfate and ammonium molybdate in sulfuric acid (CAM).

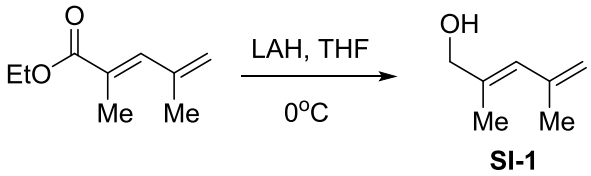
All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Toluene, tetrahydrofuran, methylene chloride, and diethyl ether were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after being purged with argon. Bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$), tricyclohexylphosphine (PCy_3), tetrapropylammonium perruthenate, and tetrakis-(triphenylphosphine) palladium(0) were purchased from Strem Chemicals, Inc. 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane (pinacolborane) was graciously donated by BASF and used without further purification. TBSOTf and TESOTf were purchased from GFS and were distilled prior to use. *Trans*-1,3-pentadiene was purchased from ChemSampCo. Ethyl 2-(triphenylphosphoranylidene)propanoate was purchased from Accela ChemBio or Aldrich. All other reagents were purchased from Aldrich, Acros or Fisher and used without further purification.

I. Preparation of Starting Materials

The protected dienols in Table 1.1 and 1.2 were prepared from the common aldehyde **SI-2**, which is available from alcohol **SI-1** *via* known ester.[46]

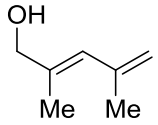


Preparation of (E)-2,4-dimethylpenta-2,4-dien-1-ol (SI-1)



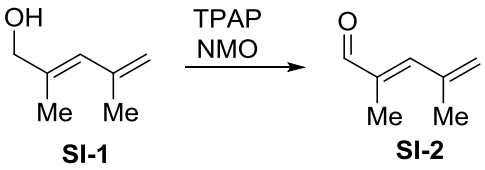
In the dry-box, a flame-dried 250 mL round-bottom flask was charged with $LiAlH_4$ (1.30 g, 33.68 mmol). The reaction flask was sealed with a septum, removed from the dry-box, and a nitrogen line was attached. The flask was cooled to 0 °C, followed by the addition of THF (66 mL). (*E*)-Ethyl-2,4-dimethylpenta-2,4-dienoate (4.33 g, 28.07 mmol) was added dropwise, and the reaction was allowed to stir for 1 h. The reaction was quenched with MeOH, followed by the addition of Rochelle's salt (30 mL), and the reaction was then allowed to stir vigorously for 2 h. The reaction mixture was diluted with Et_2O and H_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 20 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford **SI-1** a clear, colorless oil (3.09 g, 98%).

[46] Kemper, J.; Studer, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 4914.

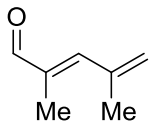


(*E*)-2,4-Dimethylpenta-2,4-dien-1-ol (SI-1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (1H, dd, *J* = 1.2 Hz, 1.2 Hz), 4.99 (1H, t, *J* = 1.6 Hz), 4.84 (1H, s), 4.04 (2H, s), 1.86 (3H, s), 1.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 136.5, 127.2, 115.3, 69.3, 23.7, 15.5; IR (neat): 3411 (br, m), 2965 (m), 2927 (m), 2874 (m), 1717 (s), 1376 (s), 1039 (s); HRMS-(ESI$^+$) for $C_7H_{13}O$ [M+H]: calculated: 113.0966, found: 113.0969.

Preparation of (E)-2,4-dimethylpenta-2,4-dienal (SI-2)



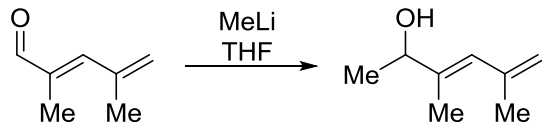
A flame-dried 250 mL round-bottom flask containing a magnetic stir bar was charged with 4Å MS, 4-methylmorpholine *N*-oxide (4.90 g, 42.00 mmol), CH_2Cl_2 (130 mL), MeCN (10 mL), and **SI-1** (3.09 g, 27.54 mmol). The reaction was allowed to stir for 20 min, then cooled to 0 ^{o}C and tetrapropylammonium perruthenate (295 mg, 0.84 mmol) was added. The reaction was allowed to stir for 2 h while warming to room temperature. The reaction mixture was concentrated by rotary evaporation, then filtered through a pad of silica gel, washing with Et_2O. The solution was concentrated to provide **SI-2** as a clear, light yellow oil (2.43 g, 80%).



(*E*)-2,4-Dimethylpenta-2,4-dienal (SI-2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.39 (1H, s), 6.71 (1H, t, *J* = 1.5 Hz), 5.32 (1H, t, *J* = 2.0 Hz), 5.26 (1H, s), 2.02 (3H, s), 1.91 (3H, d, *J* = 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.1, 152.0, 141.0, 137.8, 123.4, 22.6, 10.6; IR (neat): 3406 (br, w), 2980 (m), 2934 (m), 2875 (m),

1689 (s), 1445 (m), 1376 (m), 1023 (s); HRMS-(ESI$^+$) for $C_7H_{11}O$ [M+H]: calculated: 111.0810, found: 111.0811.

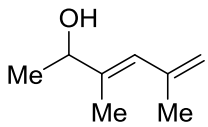
Representative procedure for organometallic nucleophile addition to aldehyde SI-2



SI-2 **1.47-H**

Preparation of (E)-3,5-dimethylhexa-3,5-dien-2-ol (1.47-H, Table 1.1)

A flame-dried 100 mL round-bottom flask containing a magnetic stir bar, under an atmosphere of nitrogen, was charged with MeLi (3.12 mL of a 1.6 M solution in Et_2O, 4.99 mmol), and Et_2O (20 mL). The reaction flask was cooled to −78 °C, and **SI-2** (500.0 mg, 4.54 mmol) was added dropwise. The reaction was allowed to stir at −78 ^oC for 1 h or until the reaction was complete by TLC. The reaction was quenched with water, and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 15 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a colorless oil (458.0 mg, 80%). R_f = 0.24 (10:1 hexanes:ethyl acetate, stain in $KMnO_4$).

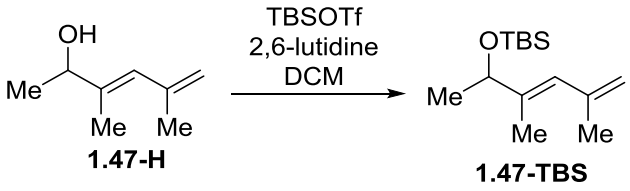


(*E*)-3,5-Dimethylhexa-3,5-dien-2-ol (1.47-H). ^1H NMR (500 MHz, $CDCl_3$): δ 5.88 (1H, d, *J* = 1.0 Hz), 4.98 (1H, q, *J* = 1.5 Hz), 4.81 (1H, t, *J* = 1.0 Hz), 4.21 (1H, q, *J* = 6.5 Hz), 1.83 (3H, s), 1.81 (3H, s), 1.26 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 140.5, 126.4, 115.2, 73.9, 23.8, 21.8, 13.4; IR (neat): 3339 (br, m), 2972 (m), 2932 (w), 2874 (w), 1443 (m), 1370 (m), 1103 (s), 954

(s); HRMS-(ESI$^+$) for $C_8H_{15}O$ [M+H]: calculated: 127.1123, found: 127.1123. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a colorless oil (458.0 mg, 80%). R_f = 0.24 (10:1 hexanes:ethyl acetate, stain in $KMnO_4$).

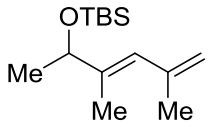
Representative procedure for TBS-protection of dienols

Preparation of (E)-tert-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (1.47-TBS, Table 1.1):

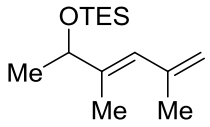


1.47-H **1.47-TBS**

A flame-dried round-bottom flask containing a magnetic stir bar, under an atmosphere of nitrogen, was charged wtih (*E*)-3,5-dimethylhexa-3,5-dien-2-ol (88.0 mg, 0.70 mmol) in CH_2Cl_2 (4 mL) and 2,6-lutidine (0.13 mL, 1.05 mmol). The reaction flask was cooled to −78 °C, followed by dropwise addition of freshly distilled TBSOTf (0.19 mL, 0.84 mmol). The reaction was allowed to stir for 1 h or until done by TLC, then quenched with water. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (136.0 mg, 81%). R_f = 0.53 (hexanes, stain in $KMnO_4$).

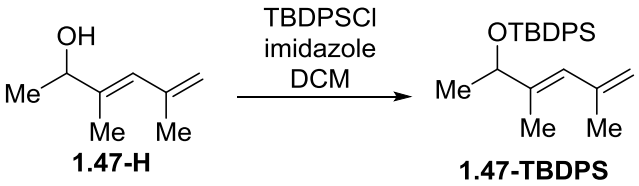


(*E*)-*tert*-Butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (1.47-TBS, Table 1.1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.84 (1H, s), 4.96 (1H, s), 4.79 (1H, s), 4.17 (1H, q, *J* = 6.5Hz), 1.85 (3H, s), 1.76 (3H, s), 1.21 (3H, d, *J* = 6.5 Hz), 0.89 (9H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.2, 131.0, 125.6, 114.6, 74.5, 26.1, 23.9, 23.5, 18.5, 13.5, -4.6, -4.7; IR (neat): 3084 (m), 2958 (m), 2887 (m), 1462 (w), 1443 (w), 1369 (w), 1254 (m), 1082 (m), 1030 (m), 995 (m), 978 (m), 864 (s), 773 (s), 549 (m); HRMS-(ESI^+) for $C_{14}H_{28}OSi$ [$M+H^+$]: calculated: 241.1988, found: 241.1977.



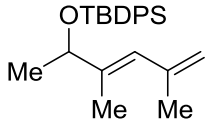
(*E*)-((3,5-Dimethylhexa-3,5-dien-2-yl)oxy)triethylsilane (1.47-TES, Table 1.1). The titled compound was synthesized according to the representative procedure for the TBS-protection of dienols but with TESOTf. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (1H, d, *J* = 1.0 Hz), 4.96 (1H, q, *J* = 1.5 Hz), 4.79 (1H, t, *J* = 1.0 Hz), 4.17 (1H, dq, *J* = 6.0 Hz, 1.0 Hz), 1.85 (3H, s), 1.77 (3H, d, *J* = 1.5 Hz), 1.23 (3H, d, *J* = 6.5 Hz), 0.95 (9H, t, *J* = 7.5 Hz), 0.59 (6H, q, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 140.9, 125.7, 114.6, 74.2, 23.9, 23.5, 13.4, 7.1, 5.0; IR (neat): 2955 (m), 2912 (m), 2877 (m), 1457 (w), 1238 (m), 1056 (s), 1004 (s), 724 (s); HRMS-(ESI^+) for $C_{14}H_{29}OSi$ [M+H]: calculated: 241.1988, found: 241.1996. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (263.0 mg, 92%). R_f = 0.42 (hexanes, stain in $KMnO_4$).

Preparation of (E)-tert-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)diphenylsilane (1.47-TBDPS, Table 1.1)



1.47-H **1.47-TBDPS**

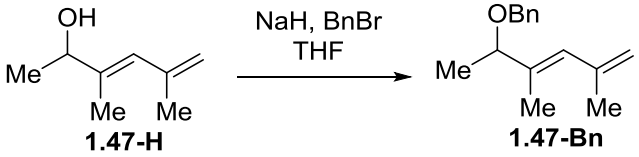
A flame-dried round-bottom flask containing a stir bar was charged with (*E*)-3,5-dimethylhexa-3,5-dien-2-ol (30.0 mg, 0.24 mmol), imidazole (19.6 mg, 0.29 mmol), and CH_2Cl_2 (1.2 mL). The reaction flask was cooled to 0 °C, then TBDPSCl (0.07 mL, 0.29 mmol) was added dropwise and the reaction was allowed to stir at 0 ^oC for 4 h. The reaction was diluted with water and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a colorless oil (60.0 mg, 68%). R_f = 0.28 (hexanes, stain in $KMnO_4$).



(*E*)-*tert*-Butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)diphenylsilane (1.47-TBDPS, Table 1.1). ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (1H, t, *J* = 1.5 Hz), 7.65 (1H, t, *J* = 1.5 Hz), 7.45-7.33 (6H, m), 5.69 (1H, s), 4.94 (1H, s), 4.73 (1H, s), 4.19 (1H, q, *J* = 6.5 Hz), 1.79 (3H, s), 1.78 (3H, t, *J* = 1.5 Hz), 1.19 (3H, dd, *J* = 6.5 Hz, 1.5 Hz), 1.08 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 140.3, 136.2, 136.1, 134.9, 134.4, 129.7, 129.6, 127.7, 127.6, 126.3, 114.5, 75.4, 27.2, 23.8, 23.3, 19.5, 13.4; IR (neat): 3071 (w), 2965 (m), 2932 (m), 2892 (w), 2858 (m), 1473 (w), 1461 (w), 1428 (m), 1389 (w), 1470 (w), 1189 (s), 1110 (s), 1079 (m), 1054 (w), 1027 (m), 891 (w), 764

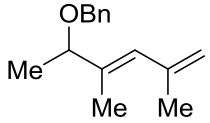
(m), 739 (m), 701 (s), 506 (s), 485 (m); HRMS-(ESI$^+$) for $C_{24}H_{33}OSi$ [M+H]: calculated: 365.2303, found: 365.2301.

Preparation of (E)-(((3,5-dimethylhexa-3,5-dien-2-yl)oxy)methyl)benzene (1.47-Bn, Table 1.1)



1.47-H **1.47-Bn**

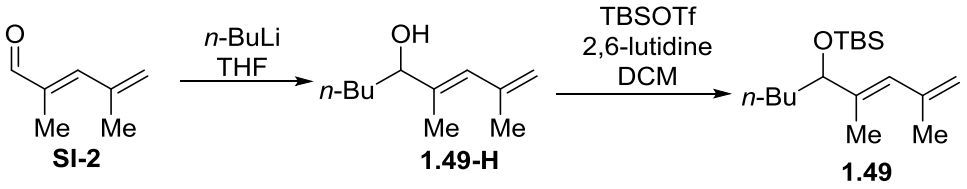
In the dry-box, a flamed-dried 25 mL 2-neck round-bottom flask was charged wtih NaH (45.0 mg, 1.90 mmol). The reaction flask was sealed with a septum, removed from the dry-box, and a nitrogen line was attached. The flask was cooled to 0 °C, followed by the addition of THF (8 mL). (*E*)-3,5-dimethylhexa-3,5-dien-2-ol (200 mg, 1.59 mmol) was then added in THF (1 mL) dropwise, and the reaction was allowed to stir for 15 min. Benzyl bromide (0.21 mL, 1.75 mmol) was then added dropwise, and the reaction was refluxed for 12 h. The reaction was diluted with water and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (256.0 mg, 75%). R_f = 0.27 (100:1 hexanes:ethyl acetate, stain in $KMnO_4$).



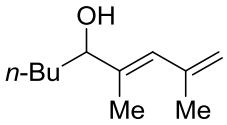
(*E*)-(((3,5-Dimethylhexa-3,5-dien-2-yl)oxy)methyl)benzene (1.47-Bn, Table 1.1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.33 (4H, m), 7.29-7.26 (1H, m), 5.88 (1H, s), 5.03 (1H, q, *J* = 1.5 Hz), 4.89 (1H, t, *J* = 1.0 Hz), 4.48

(1H, d, J = 11.5 Hz), 4.28 (1H, d, J = 12.0 Hz), 3.88 (1H, q, J = 6.4 Hz), 1.92 (3H, s), 1.83 (3H, d, J = 1.5 Hz), 1.31 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 139.1, 137.9, 129.1, 128.5, 127.9, 127.6, 115.5, 81.3, 70.0, 23.9, 20.5, 12.5; IR (neat): 3032 (m), 2980 (m), 2874 (m), 1718 (s), 1452 (s), 1269 (s), 1093 (s), 698 (s); HRMS-(ESI$^+$) for $C_{15}H_{21}O$ [M+H]: calculated: 217.1592, found: 217.1585.

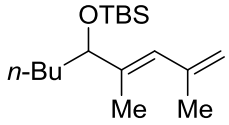
Preparation of (E)-tert-butyl((2,4-dimethylnona-1,3-dien-5-yl)oxy)dimethylsilane



The title compound was synthesized as shown above following the Representative Organometallic Nucleophile Addition Procedure with *n*-BuLi (2.5 M solution in hexanes), followed by protection using the representative TBSOTf protection procedure.

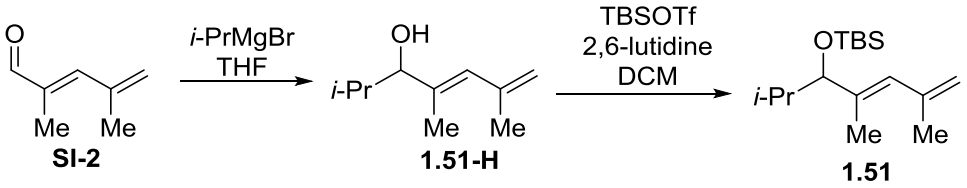


(*E*)-2,4-Dimethylnona-1,3-dien-5-ol (1.49-H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (1H, s), 5.00 (1H, q, J = 1.5 Hz), 4.83 (1H, t, J = 1.0 Hz), 4.02 (1H, t, J = 6.5 Hz), 1.86 (3H, s), 1.71 (3H, d, J = 1.5 Hz), 1.59-1.54 (2H, m), 1.37-1.32 (4H, m), 0.91 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 139.3, 127.8, 115.3, 78.5. 34.9, 28.2, 23.8, 22.8, 14.2, 13.2; IR (neat): 3353 (br, m), (2957 (s), 2930 (s), 2860 (s), 1448 (m), 1000 (s), 891 (s); HRMS-(ESI$^+$) for $C_{11}H_{21}O$ [M+H]: calculated: 169.1592, found: 169.1590. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (200 mg, 75%). R_f = 0.32 (10:1 hexanes:ethyl acetate, stain in $KMnO_4$).

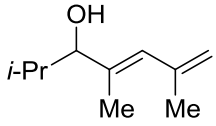


(*E*)-*tert*-Butyl((2,4-dimethylnona-1,3-dien-5-yl)oxy)dimethylsilane (Table 1.2, entry 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.78 (1H, s), 4.96 (1H, q, *J* = 1.5 Hz), 4.79 (1H, t, *J* = 1.0 Hz), 3.94 (1H, t, *J* = 6.0 Hz), 1.85 (3H, s), 1.73 (3H, d, *J* = 1.5 Hz), 1.56-1.42 (2H, m), 1.33-1.27 (4H, m), 0.91-0.86 (12H, m), 0.04 (3H, s), 0.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 140.0, 127.1, 114.5, 79.2, 36.3, 28.2, 25.9, 23.9, 22.9, 18.5, 14.3, 13.2, −4.3, −4.8; IR (neat): 2956 (s), 2930 (s), 2857 (s), 1716 (w), 1462 (m), 1254 (s), 1075 (s), 892 (s), 774 (s); HRMS-(ESI$^+$) for $C_{17}H_{35}OSi$ [M+H]: calculated: 282.2457, found: 282.2453. The crude reaction mixture was purified on silica gel (hexanes) to afford a clear, colorless oil (197 mg, 90%). R_f = 0.27 (hexanes, stain in $KMnO_4$).

Preparation of (E)-2,4,6-trimethylhepta-4,6-dien-3-ol

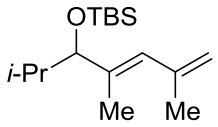


The title compound was synthesized as shown above following the representative organometallic nucleophile addition procedure with isopropylmagnesium chloride (2.0 M solution in THF), followed by protection using the representative TBSOTf protection procedure.



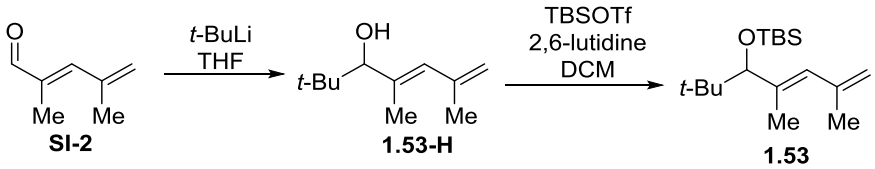
(*E*)-2,4,6-Trimethylhepta-4,6-dien-3-ol (1.51-H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (1H, s), 4.98 (1H, s), 4.81 (1H, s), 3.60 (1H, d, *J* = 13.0 Hz), 1.84 (3H, s), 1.78 (1H, m), 1.76 (3H, s), 0.97 (3H, d, *J* = 6.5 Hz), 0.80 (3H,

d, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 138.5, 129.0, 115.2, 84.5, 31.4, 23.8, 19.7, 18.6, 13.3; IR (neat): 3397 (w), 2956 (s), 2929 (s), 2859 (m), 1632 (w), 1461 (m), 1382 (m), 1297 (w), 1252 (m), 1179 (w), 1064 (s), 1015 (s), 891 (s), 836 (s), 774 (s), 670 (s), 551 (m); HRMS-(ESI$^+$) for $C_{10}H_{19}O$ [M+H]: calculated: 155.1436, found: 155.1436. The crude reaction mixture was purified by silica gel chromatography (8:1 hexanes:diethyl ether) to afford a clear, colorless oil (190.0 mg, 31%). R_f = 0.43 (4:1 hexanes: diethyl ether, stain in $KMnO_4$).

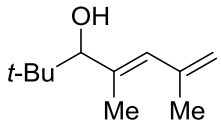


(*E*)-*tert*-Butyldimethyl((2,4,6-trimethylhepta-4,6-dien-3-yl)oxy)silane (Table 1.2, entry 2). ^{1}H NMR (500 MHz, CDCl3): δ 5.74 (1H, s), 4.97 (1H, q, J = 1.0 Hz), 4.79 (1H, d, J = 1.0 Hz), 3.52 (1H, d, J = 7.5 Hz), 1.84 (3H, s), 1.74-1.72 (4H, m), 0.91 (3H, d, J = 6.5 Hz), 0.90 (9H, s), 0.76 (3H, d, J = 7.0 Hz), 0.02 (3H, s), −0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.0, 138.9, 128.6, 114.5, 85.3, 32.4, 26.1, 23.9, 19.7, 19.2, 18.5, 13.4, −4.3, −4.8; IR (neat): 2956 (m), 2929 (m), 2857 (m), 1470 (m), 1251 (s), 1061 (s), 890 (s), 834 (s); HRMS-(ESI$^+$) for $C_{16}H_{33}OSi$ [M+H]: calculated: 269.2301, found: 269.2303. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (38.0 mg, 56%). R_f = 0.60 (hexanes, stain in $KMnO_4$).

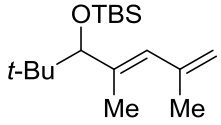
Preparation of (E)-tert-butyldimethyl((2,2,4,6-tetramethylhepta-4,6-dien-3-yl)oxy)-silane



The title compound was synthesized as shown above following the representative organometallic nucleophile addition procedure with *t*-BuLi (1.6 M solution in pentane), followed by protection using the representative TBSOTf protection procedure.



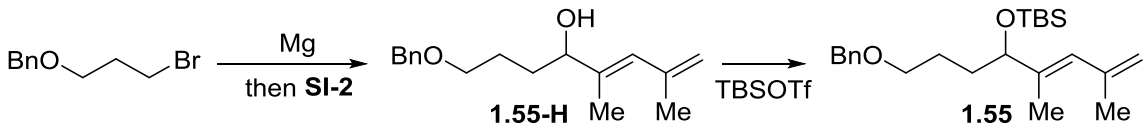
(*E*)-2,2,4,6-Tetramethylhepta-4,6-dien-3-ol (1.53-H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.83 (1H, s), 5.01 (1H, q, *J* = 1.5 Hz), 4.83 (1H, t, *J* = 1.0 Hz), 3.77 (1H, s), 1.86 (3H, d, *J* = 1.0 Hz), 1.85 (3H, d, *J* = 1.5 Hz), 0.94 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 138.3, 130.0, 115.2, 85.6, 26.9, 25.3, 24.0, 16.4; IR (neat): 3453 (br, w), 2956 (s), 2910 (s), 2871 (s), 1727 (m), 1465 (m), 1365 (s), 1059 (s); HRMS-(ESI$^+$) for $C_{11}H_{21}O$ [M+H]: calculated: 169.1592, found: 169.1597. The crude reaction mixture was purified by silica gel chromatography (20:1 hexanes:ethyl acetate) to afford a clear, colorless oil (207.0 mg, 51%). R_f = 0.30 (20:1 hexanes:ethyl acetate, stain in $KMnO_4$).



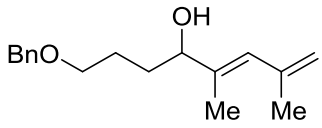
(*E*)-*tert*-Butyldimethyl((2,2,4,6-tetramethylhepta-4,6-dien-3-yl)oxy)silane (Table 3.2, entry 3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.74 (1H, s), 4.98 (1H, t, *J* = 1.5 Hz), 4.79 (1H, t, *J* = 1.0 Hz), 3.63 (1H, d, *J* = 1.0 Hz), 1.84 (3H, s), 1.77 (3H, d, *J* = 1.5 Hz), 1.08 (9H, s), 0.88 (9H, s), 0.03 (3H, s), −0.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 138.8, 129.9, 115.6, 86.4, 36.7, 27.1, 26.1, 25.9, 23.9, 18.5, −4.4, −5.2; IR (neat): 2955 (s), 2929 (m), 2858 (m), 1462 (m), 1361 (m), 1250 (m). 1076 (s), 835 (s), 774 (s); HRMS-(ESI$^+$) for $C_{17}H_{35}OSi$ [M+H]: calculated: 283.2457, found: 283.2454. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (87.0 mg, 25%). R_f = 0.73

(hexanes, stain in $KMnO_4$).

Preparation of (E)-1-(benzyloxy)-5,7-dimethylocta-5,7-dien-4-ol

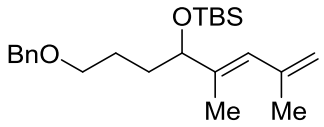


The title compound was synthesized by adding the known Grignard reagent[47] to aldehyde **SI-2** following the representative organometallic nucleophile addition procedure, followed by protection using the representative TBSOTf protection procedure.



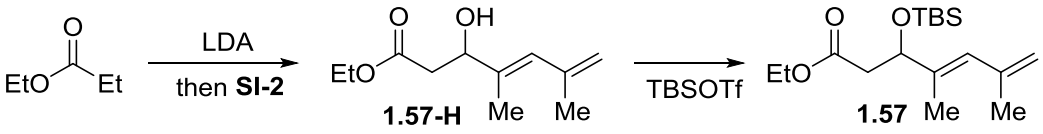
(*E*)-1-(Benzyloxy)-5,7-dimethylocta-5,7-dien-4-ol (1.55-H). ^1H NMR (500 MHz, $CDCl_3$): δ 7.36-7.33 (4H, m), 7.30-7.26 (1H, m), 5.88 (1H, s), 4.82 (1H, s), 4.52 (2H, s), 4.03 (1H, br, s), 3.53-3.50 (2H, m), 2.17-2.16 (1H, m), 1.86 (3H, s), 1.79 (3H, s), 1.73-1.64 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 139.1, 138.5, 128.6, 127.9, 127.8, 127.7, 115.3, 78.0, 73.2, 70.6, 32.5, 26.4, 23.9, 13.6; IR (neat): 3417 (w), 2938 (m), 2857 (m), 1495 (m), 1362 (m), 1309 (w), 1259 (w), 1204 (w), 1097 (s), 1054 (s) 1027 (s), 998 (s), 890 (s), 734 (s), 696 (s), 611 (m), 555 (m), 520 (m); HRMS-(ESI^+) for $C_{17}H_{25}O_2$ [M+H]: calculated: 261.1855, found: 261.1846. The crude reaction mixture was purified by silica gel chromatography (5:1 hexanes:diethyl ether) to afford a clear, colorless oil (400.0 mg, 70%). R_f = 0.33 (5:1 hexanes:ethyl acetate, stain in $KMnO_4$).

[47] Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc*. **2004**, *126*, 9536.



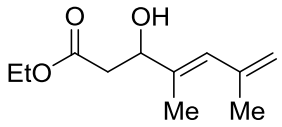
(*E*)-((1-(Benzyloxy)-5,7-dimethylocta-5,7-dien-4-yl)oxy)(*tert*-butyl)dimethylsilane (Table 1.2, entry 4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.32 (4H, m), 7.32-7.25 (1H, m), 5.78 (1H, s), 4.96 (1H, s), 4.78 (2H, s), 4.50 (2H, s), 3.97 (1H, t, *J* = 6.0 Hz), 3.49-3.44 (2H, m), 1.84 (3H, s), 1.73 (3H, s), 1.69-1.65 (1H, m), 1.60-1.53 (3H, m), 0.87 (9H, s), 0.03 (3H, s), −0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.0, 139.6, 138.9, 128.6, 127.9, 127.7, 127.3, 114.7, 78.9, 73.1, 70.1, 33.1, 26.3, 26.1, 23.9, 18.4, 13.3, −4.4, −4.8; IR (neat): 2953 (m), 2929 (m), 2855 (m), 1472 (w), 1454 (w), 1361 (w), 1254 (m), 1204 (w), 1096 (s), 1070 (s), 1028 (m), 1004 (m), 893 (m), 835 (s), 774 (s), 734 (m), 697 (m); HRMS-(ESI$^+$) for $C_{23}H_{39}O_2Si$ [M+H]: calculated: 375.2719, found: 375.2722. The crude reaction mixture was purified by silica gel chromatography (40:1 hexanes:diethyl ether) to afford a clear, colorless oil (289.0 mg, 96%). R_f = 0.41 (20:1 hexanes:diethyl ether, stain in $KMnO_4$).

Preparation of (E)-ethyl 3-((tert-butyldimethylsilyl)oxy)-4,6-dimethylhepta-4,6-dienoate

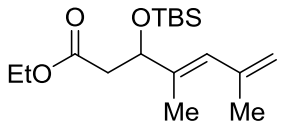


A flame-dried two-neck round-bottom flask containing a magnetic stir bar and internal thermometer was charged with dry diisopropylamine (0.28mL, 2.00 mmol) and THF (3.0 mL). The flask was cooled to −78 °C and *n*-BuLi (0.84mL, 2.00 mmol) was added dropwise. The solution was allowed to warm to 0 °C and stir for 15 min. The reaction flask was then cooled to −78 °C, and ethyl acetate (0.20 mL, 2.0 mmol, distilled) in THF (1.0 mL) was added dropwise, maintaining an internal temperature below -70 °C. The reaction was allowed to stir at −78 °C for 1.5 h, then a solution of **SI-2** (213 mg, 1.82

mmol) in THF (1.0 mL) was added dropwise at −78 °C. The reaction was allowed to stir at −78 °C for 40 min. The reaction was quenched with water (3.0 mL), diluted with ethyl acetate (10 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (3:1 hexanes:diethyl ether) to afford the title compound as a clear, colorless oil (288.0 mg, 75%). R_f = 0.51 (3:1 hexanes:ethyl acetate, stain with $KMnO_4$).



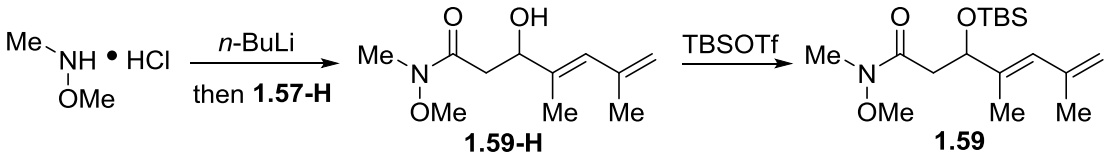
(*E*)-Ethyl 3-hydroxy-4,6-dimethylhepta-4,6-dienoate (1.57-H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.97 (1H, s), 5.01 (1H, p, *J* = 1.5 Hz), 4.83 (1H, t, *J* = 1.0 Hz), 4.46 (1H, t, *J* = 4.0 Hz), 4.18 (2H, q, *J* = 7.0 Hz), 2.85 (1H, d, *J* = 3.5 Hz), 2.58 (1H, d, *J* = 4.0 Hz), 2.56 (1H, d, *J* = 1.0 Hz), 1.85 (3H, s), 1.82 (3H, d, *J* = 1.5 Hz), 1.27 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8, 141.5, 137.0, 128.1, 115.6, 73.9, 61.0, 40.4, 23.7, 14.4, 13.9; IR (neat): 3466 (m), 3082 (w), 2981 (m), 2938 (m), 1734 (s), 1719 (s), 1445 (m), 1371 (m), 1300 (m), 1272 (s), 1178 (s), 1160 (s), 1019 (s), 894 (s), 522 (m); HRMS-(ESI$^+$) for $C_{11}H_{27}O_2$ [M-H_2O+H]: calculated: 181.1229, found: 181.1231.



(*E*)-Ethyl-3-((*tert*-butyldimethylsilyl)oxy)-4,6-dimethylhepta-4,6-dienoate (Table 3.2, entry 5). The compound was synthesized from **1.57-H** following the representative TBS-protection procedure**.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (1H, s), 4.98 (1H, s), 4.80 (1H, s), 4.50 (1H, dd, *J* = 9.0Hz, 4.5 Hz), 4.12 (2H, qd, *J* = 7.5 Hz, 7.5 Hz), 2.56 (1H, dd, *J* = 14.0 Hz, 9.0 Hz),

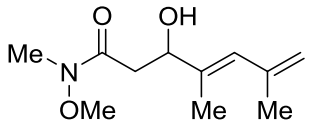
2.42 (1H, dd, J = 13.5 Hz, 4.0 Hz), 1.84 (3H, s), 1.77 (3H, s), 1.26 (3H, t, J = 7.0 Hz), 0.86 (9H, s), 0.04 (3H, s), 0.00 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.6, 141.6, 138.2, 115.3, 76.2, 60.6, 42.8, 25.9, 23.7, 18.3, 14.5, 13.0, −4.5, −5.1; IR (neat): 2956 (m), 2930 (m), 2857 (m), 1738 (s), 1472 (w), 1463 (w), 1445 (w), 1371 (m), 1273 (m), 1252 (s), 1165 (s), 1078 (s), 1024 (s), 1007 (s), 954 (m), 832 (s), 812 (m), 777 (s), 700 (m), 666 (w); HRMS-(ESI$^+$) for $C_{17}H_{33}O_3Si$ [M+H]: calculated: 313.2199, found: 313.2201. The crude reaction mixture was purified by silica gel chromatography (40:1 hexanes:diethyl ether) to afford a clear, colorless oil (198.0 mg, 84%). R_f = 0.30 (40:1 hexanes: diethyl ether, stain in $KMnO_4$).

Preparation of (E)-3-((tert-butyldimethylsilyl)oxy)-N-methoxy-N,4,6-trimethylhepta-4,6-dienamide

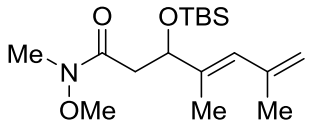


A flame- dried two-neck round-bottom flask containing a magnetic stir bar was charged with *N*,*O*-dimethylhydroxylamine hydrochloride (237.0 mg, 2.44 mmol) and THF (3.25 mL). The flask was cooled to −78 °C and *n*-BuLi (2.0 mL, 4.88 mmol in hexanes) was added dropwise at −78 °C. The reaction was allowed to warm to room temperature and stir for 10 min. The flask was then cooled to −78 °C, and **1.59-H** (120.0 mg, 0.61 mmol) in THF (1.0 mL) was added dropwise at −78 °C and allowed to stir for 2h at −78 °C. The reaction was quenched with saturated NH_4Cl (5.0 mL), diluted with ethyl acetate (10 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organics were dried over Na_2SO_4,

filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (3:1 hexanes:diethyl ether) to afford the title compound as a clear, colorless oil (100.0 mg, 89%). R_f = 0.14 (3:1 hexanes:ethyl acetate, stain with $KMnO_4$).



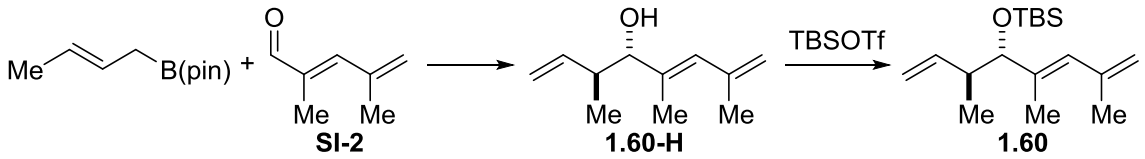
(*E*)-5-Hydroxy-2-methoxy-6,8-dimethylnona-6,8-dien-3-one (1.59-H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (1H, s), 5.00 (1H, p, *J* = 1.5 Hz), 4.84 (1H, s), 4.46 (1H, d, *J* = 8.5 Hz), 3.86 (1H, s), 3.69 (3H, s), 3.20 (3H, s), 2.71 (1H, d, *J* = 16.0 Hz), 2.61 (1H, dd, *J* = 16.5 Hz, 10.0 Hz), 1.86 (3H, s), 1.83 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 141.7, 137.3, 127.6, 115.4, 73.6, 61.5, 37.3, 32.1, 23.8, 14.3; IR (neat): 3422 (m), 2965 (m), 2921 (m), 2855 (m), 1636 (s), 1440 (s), 1385 (s), 1179 (m), 1105 (m), 997 (m), 939 (s), 890 (s), 603 (m), 524 (m), 485 (m), 432 (s); HRMS-(ESI$^+$) for $C_{11}H_{20}O_3N$ [M+H]: calculated: 214.1443, found: 214.1441.



(*E*)-3-((*tert*-Butyldimethylsilyl)oxy)-*N*-methoxy-*N*,4,6-trimethylhepta-4,6-dienamide (Table 3.2, entry 6). The compound was synthesized from **1.59-H** following the representative TBS-protection procedure**.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (1H, s), 4.98 (1H, s), 4.80 (1H, s), 4.59 (1H, dd, *J* = 9.5 Hz, 4.0 Hz), 3.71 (3H, s), 3.81 (3H, s), 2.89 (1H, t, *J* = 10.0 Hz), 2.33 (1H, dd, *J* = 13.5 Hz, 4.0 Hz), 1.84 (3H, s), 1.80 (3H, s), 0.86 (9H, s), 0.04 (3H, s), 0.00 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.8, 138.8, 127.7, 115.1, 77.6, 76.0, 61.6, 39.4, 32.2, 26.0, 23.7, 18.4, 13.5, −4.6, −4.9; IR (neat): 2955 (m), 2930 (m), 2896 (w), 2856 (m), 1664 (s), 1463 (m), 1441 (m), 1383 (s), 1250 (s), 1180 (m), 1004 (m), 972 (w), 947 (m), 892 (m), 812 (s), 777 (s), 668 (w); HRMS-(ESI$^+$) for $C_{17}H_{33}O_3NSi$ [M+H]:

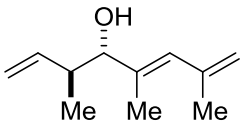
calculated: 328.2308, found: 328.2315. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:diethyl ether) to afford a clear, colorless oil (120.0 mg, 72%). R_f = 0.17 (10:1 hexanes: ethyl acetate, stain in $KMnO_4$).

Preparation of (±)-tert-butyldimethyl(((E)-3,5,7-trimethylocta-1,5,7-trien-4-yl)oxy)-silane

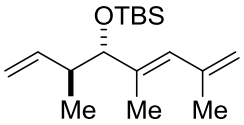


To a flame-dried 20-dram vial with stir bar was added (*E*)-2-(but-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[48] (300 mg, 1.65 mmol) followed by aldehyde **SI-2** (173 mg, 1.57 mmol) in toluene (3.2 mL). The vial was capped and heated to 60 °C and allowed to stir for 12 h. The reaction mixture was cooled to 0 °C, diluted with THF (2 mL), and 3 M NaOH (1 mL) was added. The mixture was allowed to stir for 1 h, then EtOAc (10 mL) and H_2O (10 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (50:1 hexanes:EtOAc) to afford the title compound as a clear, colorless oil (156.0 mg, 60%). R_f = 0.30 (50:1 hexanes:ethyl acetate, stain with $KMnO_4$).

[48] Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416.

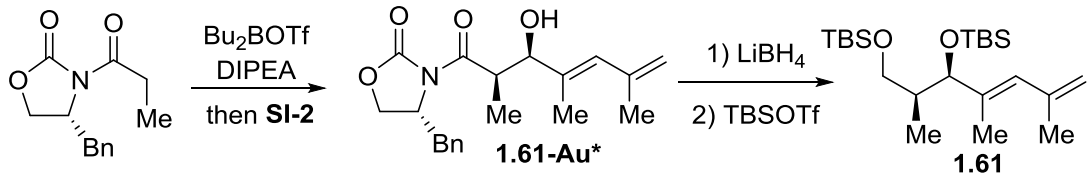


(3*S,4*S**,*E*)-3,5,7-Trimethylocta-1,5,7-trien-4-ol (1.60-H).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (1H, s), 5.75 (1H, ddd, *J* = 17.5 Hz, 10.0 Hz, 8.5 Hz), 5.21 (1H, ddd, *J* = 17.5 Hz, 2.0 Hz, 1.0 Hz), 5.17 (1H, ddd, 10.0 Hz, 2.0 Hz, 1.0 Hz), 5.01 (1H, t, *J* = 1.5 Hz), 4.84 (1H, t, *J* = 1.0 Hz), 3.67 (1H, dd, *J* = 8.5 Hz, 2.5 Hz), 2.35 (1H, ddq, *J* = 15.0 Hz, 8.0 Hz, 7.0 Hz), 1.88 (3H, s), 1.82 (3H, s), 0.92 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.6, 141.2, 136.8, 130.3, 116.8, 115.4, 81.9, 42.6, 23.8, 17.0, 13.0; IR (neat): 3424 (w), 2963 (s), 2927 (s), 2858 (m), 1637 (m), 1452 (s), 1373 (s), 1011 (s), 893 (s); HRMS-(ESI$^+$) for $C_{11}H_{19}O$ [M+H]: calculated: 167.1436, found: 167.1440.

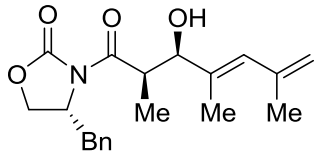


***tert*-butyldimethyl(((3*S**,4*S**,*E*)-3,5,7-trimethylocta-1,5,7-trien-4-yl)oxy)silane (Table 3.2, entry 7).** The title compound was synthesized from **1.60-H** following the representative TBS-protection procedure. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.85 (1H, ddd, *J* = 17.0 Hz, 10.5, Hz, 7.5 Hz), 5.75 (1H, s), 5.00 (1H, ddd, *J* = 10.5 Hz, 2.0 Hz, 2.0 Hz), 4.98-4.96 (1H, m), 4.97 (1H, s), 4.78 (1H, s), 3.67 (1H, d, *J* = 7.5 Hz), 2.31 (1H, ddq, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz), 1.83 (3H, s), 1.74 (3H, s), 0.92-0.83 (12H, m), 0.22 (3H, s), −0.03 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.1, 141.9, 138.4, 128.9, 114.7, 114.0, 83.6, 42.4, 26.1, 23.8, 18.5, 16.8, 13.4, −4.3, −4.8; IR (neat): 2962 (s), 2929 (s), 2858 (s), 1636 (w), 1452 (m), 1252 (m), 1066 (s), 833 (s), 773 (s); HRMS-(ESI$^+$) for $C_{17}H_{33}OSi$ [M+H]: calculated: 281.2301, found: 281.2296. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (288 mg, 85%). R_f = 0.40 (hexanes, stain in $KMnO_4$).

Preparation of (5R,6S)-2,2,3,3,6,9,9,10,10-nonamethyl-5-((E)-4-methylpenta-2,4-dien-2-yl)-4,8-dioxa-3,9-disilaundecane



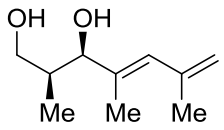
To a flame-dried 100 mL round-bottom flask with magnetic stir bar was added (*R*)-4-benzyl-3-propionyloxazolidin-2-one then was purged with N_2. The flask was cooled to 0 °C and CH_2Cl_2 (20 mL) and diisopropylethylamine (1.33 mL, 7.62 mmol) were added, followed by the dropwise addition of dibutylboryl trifluoromethanesulfonate (6.5 mL of a 1.0 M solution in CH_2Cl_2, 6.54 mmol). The reaction mixture was allowed to stir at 0 °C for 1 h then cooled to −78 °C. Aldehyde **SI-2** (600 mg, 5.45 mmol) was then added and the reaction was allowed to stir for 30 min. The reaction mixture was warmed to 0 °C and allowed to stir for an additional 1 h, followed by the addition of pH=7 buffer (5 mL), MeOH (5 mL), and H_2O_2 (5 mL). The reaction mixture was allowed to stir for 1 h, warming to room temperature, then diluted with EtOAc (50 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (4:1 hexanes:EtOAc) to afford the title compound as a clear, yellow oil (1.44 g, 77%). R_f = 0.10 (4:1 hexanes:ethyl acetate, stain with $KMnO_4$).



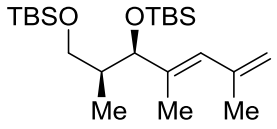
(*R*)-4-Benzyl-3-((2*R*,3*R*,*E*)-3-hydroxy-2,4,6-trimethylhepta-4,6-dienoyl)oxazolidin-2-one (1.61-Au*). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.32 (2H, m), 7.30-7.28 (1H, m), 7.22-7.20 (2H, m), 6.05 (1H, d, *J* = 1.0 Hz), 5.00 (1H, t, *J* = 1.5 Hz), 4.82 (1H, t, *J* = 1.0 Hz), 4.70 (1H, m), 4.40 (1H, s, br), 4.24-4.17 (2H, m), 4.02 (1H, dddd, *J* = 7.0 Hz, 3.5 Hz, 3.5 Hz, 3.5 Hz), 3.27 (1H, dd, *J* = 13.5 Hz, 3.5 Hz), 2.93 (1H, d, *J* = 3.0 Hz), 2.80 (1H, dd, *J* = 13.5 Hz, 9.5 Hz), 1.86 (3H, s), 1.79 (3H, d, *J* = 0.50 Hz), 1.21 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1, 152.9, 141.5, 135.0, 129.6, 129.2, 128.0, 127.7, 115.2, 75.4, 66.2, 55.3, 40.3, 37.8, 23.7, 15.2, 10.4; IR (neat): 3508 (w), 3083 (w), 3028 (w), 2972 (w), 1776 (s), 1696 (s), 1382 (s), 1209 (s), 1108 (s), 702 (s). HRMS-(ESI$^+$) for $C_{20}H_{24}NO_3$ [M+H-H_2O]: calculated: 326.1756, found: 326.1753. $[\alpha]_D^{22}$ = −33.9 (c = 1.2, $CHCl_3$, l = 50 mm).

A 20-dram vial containing a magnetic stir bar was charged with **1.61-Au***, MeOH (0.02 mL), and THF (1.8 mL) then sealed with a septum and cooled to 0 °C. Lithium borohydride (0.22 mL of a 2.0 M solution in tetrahydrofuan, 0.44 mmol) was added dropwise and the reaction was allowed to stir for 1 h. The reaction was quenched with H_2O (2 mL) followed by the addition of saturated potassium sodium tartrate solution (5 mL) and the reaction mixture was allowed to stir for 3 h. The reaction was diluted with EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel

chromatography (1:1 hexanes:EtOAc) to afford the title compound as a clear, yellow oil (73 mg, 98%). R_f = 0.2 (1:1 hexanes:ethyl acetate, stain with $KMnO_4$).



(2*S*,3*R*,*E*)-2,4,6-Trimethylhepta-4,6-diene-1,3-diol (1.61-OH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.92 (1H, d, *J* = 1.0 Hz), 4.99 (1H, t, *J* = 1.5 Hz), 4.80 (1h, t, *J* = 1.5 Hz), 4.16 (1H, d, *J* = 4.0 Hz), 3.65 (2H, d, *J* = 5.5 Hz), 2.56 (1H, s, br), 2.02 (3H, s), 1.90 (1H, dqd, *J* = 7.0 Hz, 5.5 Hz, 4.0 Hz), 1.85 (3H, s), 1.75 (3H, d, *J* = 1.5Hz), 0.88 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 137.8, 127.1, 115.0, 78.9, 66.9, 37.8, 24.0, 15.2, 10.5; IR (neat): 3373 (s), 2966 (s), 2932 (s), 2876 (s), 1743 (m), 1629 (w), 1450 (s), 1375 (s), 1030 (s), 892 (s). HRMS-(ESI$^+$) for $C_{10}H_{19}O_2$ [M+H]: calculated: 171.1385, found: 171.1390. $[\alpha]_D^{22}$ = +18.4 (c = 1.0, $CHCl_3$, l = 50 mm).



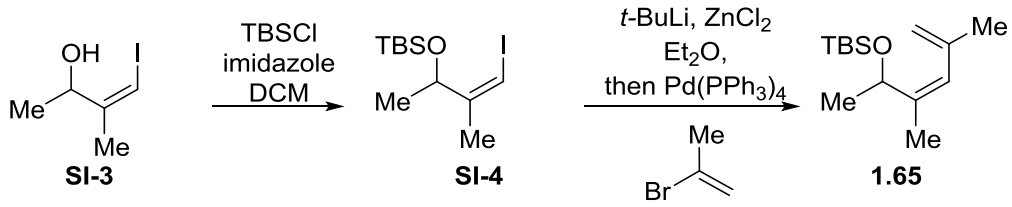
(5*R*,6*S*)-2,2,3,3,6,9,9,10,10-Nonamethyl-5-((*E*)-4-methylpenta-2,4-dien-2-yl)-4,8-dioxa-3,9-disilaundecane (Table 1.2, Entry 8). The title compound was synthesized from **1.61-OH** following the representative TBS-protection procedure**.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.82 (1H, s), 4.96 (1H, dd, *J* = 2.0 Hz, 2.0 Hz), 4.77 (1H, s), 3.98 (1H, d, *J* = 5.5 Hz), 3.47 (1H, dd, *J* = 10.0 Hz, 6.0 Hz), 3.51 (1H, dd, *J* = 10.0 Hz, 6.0 Hz), 1.81 (3H, s), 1.75-1.70 (1H, m), 1.71 (3H, d, *J* = 1.5 Hz), 0.90 (9H, s), 0.89 (9H, s), 0.04 (3H, s), 0.02 (3H, s), 0.02 (3H, s), −0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ142.1, 138.3, 127.8, 114.3, 78.4, 65.5, 40.1, 26.1, 26.1, 24.1, 18.5, 14.5, 12.0, −4.3, −4.95, −5.0, −5.2; IR (neat); 2956 (s), 2928 (s), 2857 (s), 1471 (m), 1388 (w), 1252 (s), 1060 (s), 835 (s), 774 (s). HRMS-(ESI$^+$) for $C_{22}H_{47}O_2Si_2$ [M+H]:

calculated: 399.3115, found: 399.3119. $[\alpha]_D^{22}$ = +10.0 (c = 1.0, $CHCl_3$, l = 50 mm). The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (104.0 mg, 35%). R_f = 0.47 (hexanes, stain in $KMnO_4$).

For preparation and characterization data of compound **1.63** (Table 1.2, Entry 9), see supporting information of Chapter 2.

Preparation of (Z)-tert-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane

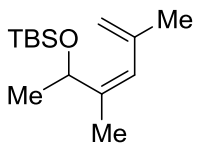
The title compound was synthesized as shown in the scheme below from the known alcohol **SI-3**.[49]



A flame-dried 6-dram vial containing a magnetic stir bar, under nitrogen, was charged with *t*-BuLi (1.6 mL of a 1.6 M solution in pentane, 2.56 mmol) and Et_2O (1.5 mL). The vial was cooled to −78 °C and 2-bromopropene (0.20 mL, 1.28 mmol) was added dropwise. The reaction was allowed to stir for 30 min at −78 °C, then $ZnCl_2$ (174.5 mg, 1.28 mmol) in THF (3 mL) was added. The reaction was allowed to warm to room temperature and stir for 30 min. The reaction mixture was then transferred *via* cannula to a separate flame-dried 6-dram vial, with a magnetic stir bar, containing $Pd(PPh_3)_4$ (37 mg, 0.032 mmol), **SI-4** (209.0 mg, 0.64 mmol), and THF (2 mL). The reaction was allowed to stir at room temperature for 12 h, followed by filtration through a pad of silica gel, washing with Et_2O. The solution was concentrated by rotary evaporation and the

[49] Skepper, C. K.; Quach, T.; Molinski, T. F. *J. Am. Chem. Soc*. **2010**, *132*, 10286.

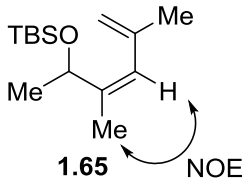
crude reaction mixture was purified by silica gel chromatography (400:1 hexanes:ethyl acetate) to afford a clear, colorless oil (104.0 mg, 68%). R_f = 0.50 (400:1 hexanes:ethyl acetate, stain in $KMnO_4$). The product contains ~10% (*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane.



(*Z*)-*tert*-Butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (Table 1.3, entry 1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.55 (1H, t, *J* = 1.0 Hz), 4.97 (1H, q, *J* = 6.5 Hz), 4.95 (1H, t, *J* = 1.5 Hz), 4.61 (1H, q, *J* = 1.5 Hz), 1.79 (3H, t, *J* = 1.0 Hz), 1.75 (3H, d, *J* = 1.5 Hz), 1.23 (3H, d, *J* = 6.5 Hz), 0.87 (9H, s), 0.00 (3H, s), -0.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 141.6, 126.5, 113.9, 66.4, 26.1, 24.0, 23.4, 18.4, 17.5, −4.8, −4.8; IR (neat): 2955 (m), 2929 (m), 2857 (m), 1471 (m), 1252 (s), 1078 (s), 832 (s), 773 (s); HRMS-(ESI$^+$) for $C_{14}H_{29}OSi$ [M+H]: calculated: 241.1988, found: 241.1998.

Proof of Stereochemistry

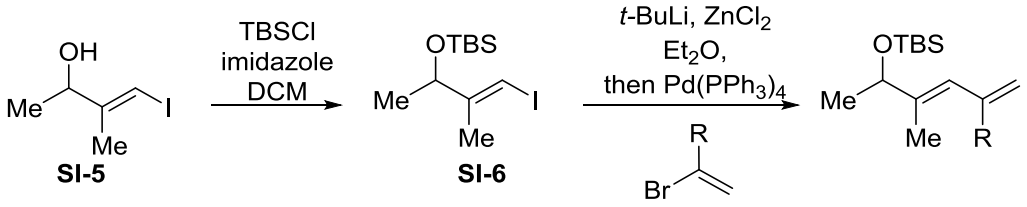
(*Z*)-alkene stereochemistry was proven by NOE correlation as shown below.



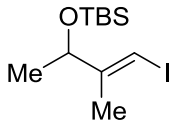
Preparation of Dienes in Table 1.3

The dienes in Table 1.3 (entries 2-4) were prepared from the common vinyl iodide **SI-6**, which is available from the known alcohol **SI-5**.[50]

[50] Alvarez, R.; Herrero, M.; López, S.; de Lera, A. R. *Tetrahedron* **1998**, *54*, 6793.

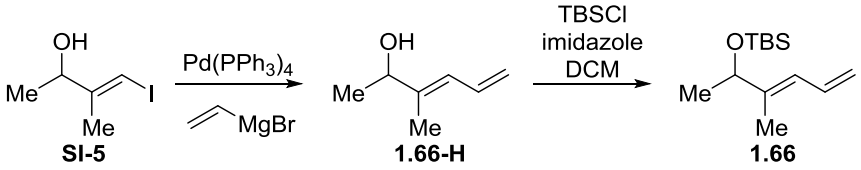


A flame-dried 50 mL round-bottom flask containing a magnetic stir bar was cooled to 0 °C and charged wtih (*E*)-4-iodo-3-methylbut-3-en-2-ol **SI-5** (1.07 g, 5.05 mmol), CH_2Cl_2 (16 mL), imidazole (378.0 mg, 5.55 mmol), and TBSCl (837.0 mg, 5.55 mmol). The reaction was allowed to stir for 12 h, warming to room temperature. The reaction was diluted with water and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation.

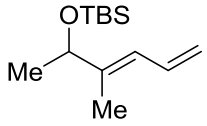


(*E*)-*tert*-Butyl((4-iodo-3-methylbut-3-en-2-yl)oxy)dimethylsilane (SI-6). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (1H, s), 4.30 (1H, q, *J* = 6.0 Hz), 1.79 (3H, d, *J* = 1.2 Hz), 1.21 (3H, d, *J* = 6.0 Hz), 0.88 (9H, s), 0.04 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 76.9, 73.3, 26.0, 23.4, 20.1, 18.4, −4.8, −4.8; IR (neat): 2954 (m), 2929 (m), 2857 (m), 1471 (w), 1252 (m), 1088 (s), 834 (s), 775 (s); HRMS-(ESI$^+$) for $C_{11}H_{27}INOSi$ [M+NH_4]: calculated: 344.0907, found: 344.0919. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (1.38 g, 84%). R_f = 0.48 (hexanes, stain in $KMnO_4$).

Preparation of (E)-tert-butyldimethyl((3-methylhexa-3,5-dien-2-yl)oxy)silane



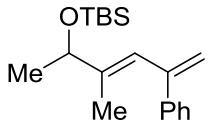
In the dry-box, a flame-dried round bottom flask containing a magnetic stir bar, was charged with $Pd(PPh_3)_4$ (54.5 mg, 0.05 mmol). The flask was sealed with a septum, removed from the box and cooled to 0 °C. (*E*)-4-Iodo-3-methylbut-3-en-2-ol **SI-5** (200 mg, 0.94 mmol) in toluene (6.8 mL) was then added and allowed to stir for 20 min, followed by the dropwise addition of vinyl magnesium bromide (2.82 mL, 1.0 M in THF, 2.82 mmol). The solution was allowed to stir for 1 h at 0 °C, then was warmed to room temperature and allowed to stir for an additional 30 min. The reaction was quenched with a saturated solution of ammonium chloride (5 mL) followed by the addition of water (5 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL), and the combined organics were dried over Na_2SO_4 and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (44.0 mg, 42%). The representative procedure for TBS-protection of dienols was used to make the titled diene **1.66**.



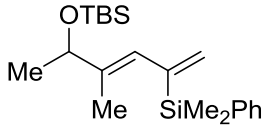
(*E*)-*tert*-Butyldimethyl((3-methylhexa-3,5-dien-2-yl)oxy)silane (Table 1.3, entry 2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.58 (1H, dt, *J* = 17.0 Hz, 11.0 Hz), 6.19 (1H, d, *J* = 11.0 Hz), 5.16 (1H, dd, *J* = 17.0 Hz, 2.5 Hz), 5.06 (1H, dd, *J* = 10.0 Hz, 2.0 Hz), 4.20 (1H, q, *J* = 6.5 Hz), 1.73 (3H, d, *J* = 1.0 Hz), 1.21 (3H, d, *J* = 6.5 Hz), 0.89 (9H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.7, 133.3, 124.1, 73.7, 26.1, 26.0, 23.4, 18.5, 12.4, −4.6, −4.7; HRMS-(ESI$^+$) for $C_{13}H_{27}OSi$ [M+H]: calculated: 227.1831, found: 227.1842. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (55.0 mg, 62%). R_f = 0.34 (hexanes, stain in $KMnO_4$).

Representative procedure for Negishi cross-coupling

A flame-dried 6-dram vial containing a magnetic stir bar, under an atmosphere of nitrogen, was charged with *t*-BuLi (2.2 mL of a 1.6 M solution in pentane, 3.50 mmol) and Et_2O (2 mL). The vial was cooled to −78 °C and α-bromostyrene (0.23 mL, 1.75 mmol) was added dropwise. The reaction was allowed to stir for 30 min at −78 °C, then $ZnCl_2$ (238 mg, 1.75 mmol) in THF (2 mL) was added. The reaction was allowed to warm to room temperature and stir for 30 min. The reaction mixture was then transferred via cannula to a separate flame-dried 6-dram vial, containing a magnetic stir bar, $Pd(PPh_3)_4$ (67.0 mg, 0.060 mmol), **SI-6** (380.0 mg, 1.16 mmol), and THF (2 mL). The reaction was allowed to stir at room temperature for 12 h, followed by filtration through a pad of silica gel, washing with Et_2O. The solution was concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (248.0 mg, 70%). R_f = 0.38 (hexanes, stain in $KMnO_4$).



(*E*)-*tert*-Butyldimethyl((3-methyl-5-phenylhexa-3,5-dien-2-yl)oxy)silane (Table 1.3, entry 3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.37 (2H, m), 7.34- 7.24 (3H, m), 6.17 (1H, s), 5.56 (1H, d, *J* = 1.6 Hz), 5.10 (1H, t, *J* = 1.6 Hz), 4.30 (1H, q, *J* = 6.4 Hz), 1.66 (3H, d, *J* = 1.2 Hz), 1.28 (3H, d, *J* = 6.4 Hz), 0.92 (9H, s), 0.09 (3H, s), 0.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.1, 144.0, 141.4, 128.4, 127.6, 126.7, 123.5, 114.9, 74.0, 26.1, 23.7, 18.5, 13.8, −4.5, −4.7; IR (neat): 3082 (w), 3026 (m), 2929 (m), 1462 (w), 1250 (m), 1084 (s), 834 (s), 774 (s), 703 (s); HRMS-(ESI$^+$) for $C_{19}H_{31}OSi$ [M+H]: calculated: 303.2144, found: 303.2129.



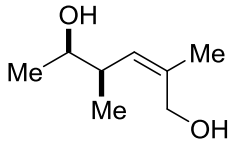
(*E*)-*tert*-Butyl((5-(dimethyl(phenyl)silyl)-3-methylhexa-3,5-dien-2-yl)oxy)dimethylsilane (Table 1.3, entry 4). The title compound was synthesized following the representative Negishi cross-coupling procedure with (1-bromovinyl)dimethyl(phenyl)silane.[51] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.49 (2H, m), 7.35-7.32 (3H, m), 5.94 (1H, s), 5.60 (1H, dd, *J* = 3.6 Hz, 2.0 Hz), 5.54 (1H, dd, *J* = 3.6 Hz, 1.2 Hz), 4.15 (1H, q, *J* = 6.4 Hz), 1.60 (3H, d, *J* = 1.2 Hz), 1.18 (3H, d, *J* = 6.4 Hz), 0.85 (9H, s), 0.35 (6H, s), 0.00 (3H, s), −0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ148.2, 140.2, 138.2, 134.2, 129.2, 128.0, 127.9, 125.1, 74.0, 26.1, 23.7, 18.4, 12.9, −3.0, −3.1, −4.6, −4.8; IR (neat): 2955 (m), 2928 (m), 2857 (w), 1471 (w), 1248 (s), 1083 (s), 1053 (s), 832 (s), 773 (s), 773 (s), 698 (s); HRMS-(ESI$^+$) for $C_{21}H_{35}OSi_2$ [M+H]: calculated: 359.2226, found: 359.2231. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (648.0 mg, 95%). R_f = 0.23 (hexanes, stain in $KMnO_4$). The purified product was not reactive in the hydroboration reaction. To further purify, the product was heated with a heat gun while under vacuum to remove any volatiles. The oil was then filtered through a pad of silica gel, washing with hexanes. The resulting diene was a 3:1 *E:E* to *E:Z* mixture.

II. Representative Procedure for Diene Hydroboration/Oxidation & Full Characterization and Proof of Stereochemistry

In the dry-box, an oven-dried 6-dram vial containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (0.20 mL of a 31.30 μM solution of $Ni(cod)_2$ in THF, 6.20 μmol), PCy_3 (0.2 mL of a 31.3 0 μM solution of PCy_3 in THF, 6.20 μmol), THF (1.00 mL, 0.25M), pinacolborane (33.5 mg, 0.26 mmol), and (*E*)-*tert*-butyl((3,5-

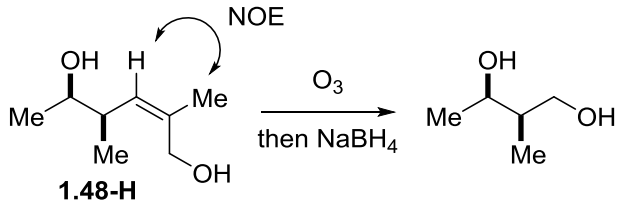
[51] Anderson, J. C.; Smith, S. C.; Swarbrick, M. E. *J. Chem. Soc., Perkin Trans*. **1997**, *1*, 1517.

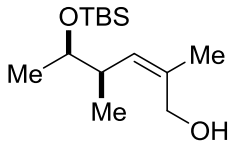
dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (60 mg, 0.25 mmol). The vial was sealed with a polypropylene cap, removed from the dry-box, immediately cooled to °C (ice/water), and allowed to stir for 3 h. The reaction mixture was kept at 0 °C and charged with 3 M sodium hydroxide (1 mL), and 30% hydrogen peroxide (0.75 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (1 mL) was added dropwise. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography.



***syn*-(*Z*)-2,4-Dimethylhex-2-ene-1,5-diol (Table 1.1, entry 10).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.09 (1H, d, *J* = 11.5 Hz), 4.20 (1H, d, *J* = 11.5 Hz), 3.79 (1H, d, *J* = 11.5 Hz), 3.66 (1H, qd, *J* = 6.5 Hz, 6.5 Hz), 2.66-2.62 (1H, m), 1.80 (3H, s), 1.05 (3H, d, *J* = 6.5 Hz), 0.91 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.9, 129.6, 71.4, 61.5, 38.6, 22.7, 18.3, 17.9; IR (neat): 3315 (m), 2967 (m), 2930 (m), 2873 (m), 1450 (m), 1375 (m), 1316 (w), 1192 (w), 1155 (w), 1087 (m), 1003 (s), 949 (m), 932 (m), 901 (m), 866 (w), 602 (m), 559 (m); HRMS-(ESI$^+$) for $C_8H_{18}O_2$ [M+H]: calculated: 145.1229, found: 145.1225. The crude reaction mixture was purified by silica gel chromatography (1:1 hexanes:diethyl ether) to afford a clear, colorless oil (47.0 mg, 56%, 6:1 dr). R_f = 0.19 (1:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to known diol[52] by ozonolysis/reduction.

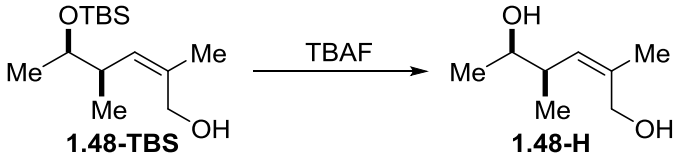




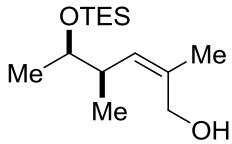
***syn*-(*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylhex-2-en-1-ol (Table 1.1, entry 5).** ^{1}H NMR (500 MHz, C_6D_6): δ 5.03 (1H, d, *J* = 10.0 Hz), 4.01 (1H, d, *J* = 12.0 Hz), 3.90 (1H, d, *J* = 11.5 Hz), 3.51 (1H, quin, *J* = 6.0 Hz), 2.48 (1H, ddq, *J* = 10.0 Hz, 7.0 Hz, 5.5 Hz), 1.78 (3H, d, *J* = 1.5 Hz), 1.03 (3H, d, *J* = 6.5 Hz), 0.99 (9H, s), 0.96 (3H, d, *J* = 7.0 Hz), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (125 MHz, C_6D_6): δ 136.1, 131.1, 73.6, 62.1, 40.5, 26.5, 22.4, 21.4, 18.8, 18.2, −3.9, −4.3; IR (neat): 3334 (br, w), 2957 (m), 2929 (m), 2856 (m), 1462 (w), 1253 (s), 1093 (s), 1005 (s), 959 (s), 834 (s), 773 (s); HRMS-(ESI$^+$) for $C_{14}H_{31}O_2Si$ [M+H]: calculated: 259.2093, found: 259.2089. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (57.0 mg, 89%, 14:1 dr). R_f = 0.24 (10:1 hexanes:ethyl acetate, stain in PMA).

[52] Dandapani, S.; Jeske, M.; Curran, D. P. *J. Org. Chem*. **2005**, *70*, 9447.

Proof of Stereochemistry: (*Z*)-alkene and *syn*-stereochemistry were proven by comparison to (*Z*)-2,4-dimethylhex-2-ene-1,5-diol (Table 1.1, entry 10) after deprotection as shown below.

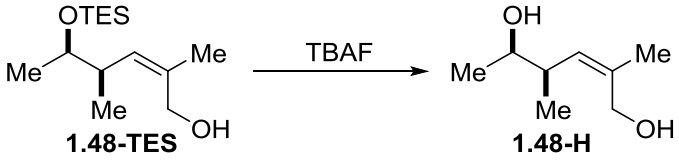


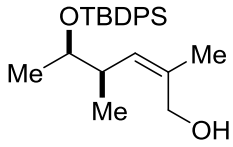
1.48-TBS **1.48-H**



***syn*-(*Z*)-2,4-Dimethyl-5-((triethylsilyl)oxy)hex-2-en-1-ol (Table 1.1, entry 7).** ^{1}H NMR (500 MHz, C_6D_6): δ 5.04 (1H, ddd, *J* = 10.0 Hz, 1.5 Hz, 1.0 Hz), 4.12 (1H, d, *J* = 11.5 Hz), 3.89 (1H, d, *J* = 12.0 Hz), 3.56 (1H, dq, *J* = 6.0 Hz, 5.0 Hz), 2.57 (1H, ddq, *J* = 10.0 Hz, 7.0 Hz, 5.0 Hz), 1.82 (3H, d, *J* = 1.5 Hz), 1.03 (3H, d, *J* = 6.0 Hz), 1.00 (9H, t, *J* = 8.0 Hz), 0.94 (3H, d, *J* = 8.0 Hz), 0.61 (6H, q, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, C_6D_6): δ 137.1, 130.4, 73.5, 62.1, 40.4, 22.7, 20.5, 18.4, 7.5, 5.6; IR (neat): 3322 (br, w), 2957 (s), 2930 (s), 2856 m), 1472 (m), 1251 (s), 1085 (s), 1050 (s), 938 (s), 771 (s); HRMS-(ESI^{+}) for $C_{14}H_{31}O_2Si$ [M+H]: calculated: 259.2093, found: 259.2090. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (61.3 mg, 95%, 12:1 dr). R_f = 0.30 (10:1 hexanes:ethyl acetate, stain in PMA).

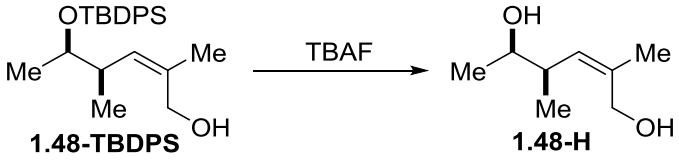
Proof of Stereochemistry: (*Z*)-alkene and *syn*-stereochemistry were proven by comparison to (*Z*)-2,4-dimethylhex-2-ene-1,5-diol (Table 1.1, entry 10) after deprotection as shown below.

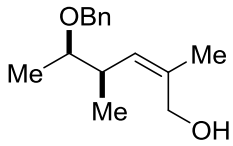




***syn*-(*Z*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2,4-dimethylhex-2-en-1-ol (Table 1.1, entry 8)**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70-7.67 (4H, m), 7.44-7.35 (6H, m), 5.17 (1H, d, *J* = 10.5 Hz), 4.07 (1H, d, *J* = 11.5 Hz), 4.00 (1H, d, *J* = 12.0 Hz), 3.72 (1H, quin, *J* = 6.5 Hz), 2.55 (1H, dqd, *J* = 10.0 Hz, 6.5 Hz, 6.5 Hz), 1.79 (3H, s), 1.06 (9H, s), 0.94 (3H, d, *J* = 6.5 Hz), 0.94 (3H, d, *J* =7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.2, 136.1, 135.0, 134.7, 134.3, 131.6, 130.0, 129.7, 127.7, 127.6, 74.1, 62.2, 39.7, 27.3, 21.8, 20.4, 19.6, 17.5; IR (neat): 3341 (w), 3071 (w), 2964 (m), 2931 (m), 2858 (m), 1472 (w), 1427 (m), 1376 (w), 1109 (s), 1007 (s), 958 (m), 739 (m), 701 (s), 688 (m), 611 (m), 505 (s), 488 (m); HRMS-(ESI^+) for $C_{24}H_{35}O_2Si$ [M+H]: calculated: 383.2406, found: 383.2408. The crude reaction mixture was purified by silica gel chromatography (2:1 hexanes:diethyl ether) to afford a clear, colorless oil (28.0 mg, 80%, >20:1 dr). R_f = 0.48 (1:1 hexanes:diethyl ether, stain in PMA).

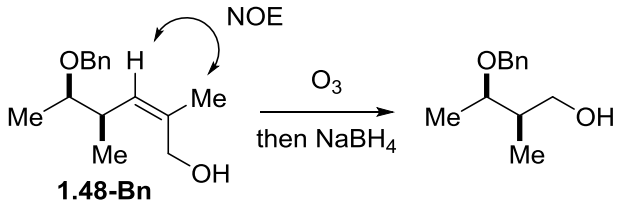
Proof of Stereochemistry: (*Z*)-alkene geometry and *syn*-stereochemistry were proven by comparison to (*Z*)-2,4-dimethylhex-2-ene-1,5-diol (Table 1.1, entry 1) after deprotection as shown below.

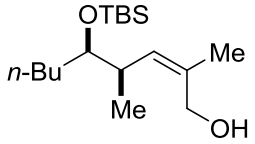




***syn*-(*Z*)-5-(Benzyloxy)-2,4-dimethylhex-2-en-1-ol (Table 1.1, entry 9).** The reaction was performed with the representative procedure but for 12 h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.34 (4H, m), 7.32-7.26 (1H, m), 5.10 (1H, d, *J* = 10.0 Hz), 4.61 (1H, d, *J* = 11.5 Hz), 4.46 (1H, d, *J* = 11.5 Hz), 3.77 (1H, br, d, *J* = 11.0 Hz), 3.40 (1H, quin, *J* = 6.5 Hz), 2.8-2.75 (1H, m), 2.50 (1H, br, s), 1.82 (3H, s), 1.11 (3H, d, *J* = 6.0 Hz), 0.96 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.4, 136.8, 129.9, 128.6, 128.1, 127.9, 79.1, 70.9, 61.8, 37.3, 22.7, 18.3, 14.8; IR (neat): 3395 (m), 2968 (m), 2929 (m), 2870 (m), 1452 (m), 1474 (m), 1203 (w), 1094 (s), 1064 (s), 1005 (s), 947 (w), 929 (w), 865 (w), 735 (s), 697 (s), 610 (w); HRMS-(ESI$^+$) for $C_{15}H_{23}O_2$ [M+H]: calculated: 235.1698, found: 235.1720. The crude reaction mixture was purified by silica gel chromatography (2:1 hexanes:diethyl ether) to afford a clear, colorless oil (46.8 mg, 72%, 7:1 dr). R_f = 0.35 (1:1 hexanes:diethyl ether, stain in PMA).

***Proof of Stereochemistry*:** (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to known compound[53] by ozonolysis/reduction.

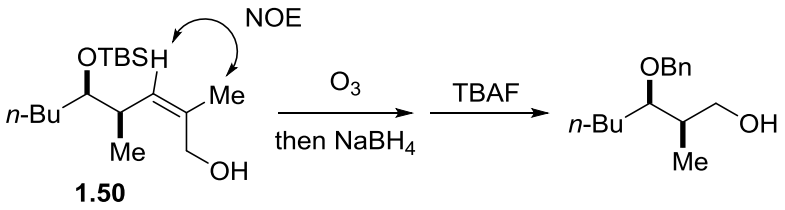


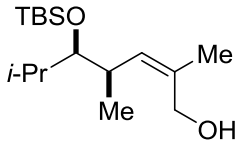


***syn*-(*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethylnon-2-en-1-ol (Table 1.2, entry 1).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.16 (1H, d, *J* = 10.0 Hz), 4.11 (1H, d, *J* = 11.5 Hz), 4.04 (1H, d, *J* = 11.5 Hz), 3.47 (1H, dt, *J* = 6.0 Hz, 4.5 Hz), 2.55 (1H, ddq, *J* = 10.0 Hz, 7.0 Hz, 4.5 Hz), 1.80 (3H, d, *J* = 1.5 Hz), 1.62 (1H, br, s), 1.48-1.34 (2H, m), 1.30-1.23 (4H, m), 0.93 (3H, d, *J* = 7.0 Hz), 0.90 (9H, s), 0.88 (3H, t, *J* = 7.0 Hz), 0.05 (3H, s), 0.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.1, 132.3, 77.0, 62.0, 37.5, 34.3, 27.7, 26.3, 23.2, 21.9, 18.5, 17.2, 14.3, −4.1, −4.2; IR (neat): 3335 (br, w), 2956 (s), 2930 (s), 2858 (s), 1461 (m), 1253 (s), 1005 (s), 834 (s), 773 (s); HRMS-(ESI$^+$) for $C_{17}H_{37}O_2Si$ [M+H]: calculated: 301.2563, found: 301.2570. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (57.3 mg, 92%, >20:1 dr). R_f = 0.41 (10:1 hexanes:ethyl acetate, stain in PMA).

[53] Roush, W. R.; Marron, T. G.; Pfeifer, L. A. *J. Org. Chem*. **1997**, *62*, 474.

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. The relative configuration was assigned by comparison of the ^{1}H NMR spectrum with the known diol,[54] after conversion of the title compound to the known diol by ozonolysis/reduction/deprotection as shown below.

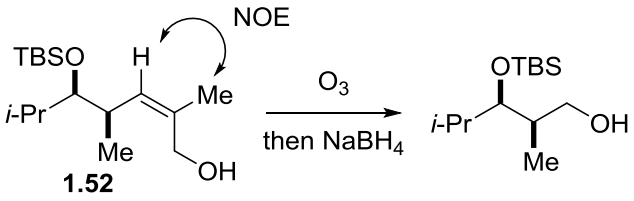


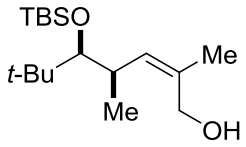


***syn*-(*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4,6-trimethylhept-2-en-1-ol (Table 1.2, entry 2).** The reaction was performed with the representative procedure but for 12 h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (1H, d, *J* = 10.0 Hz), 4.10 (2H, s), 3.19 (1H, t, *J* = 4.5 Hz), 2.58 (1H, qdd, *J* = 12.5Hz, 4.0 Hz, 4.0 Hz), 1.78 (3H, s), 1.76-1.68 (1H, m), 0.93 (3H, d, *J* = 6.0 Hz), 0.91 (9H, s), 0.88 (3H, d, *J* = 7.5 Hz), 0.83 (3H, d, *J* = 6.0 Hz), 0.04 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.3, 133.0, 81.8, 62.1, 36.5, 32.1, 26.5, 21.7, 20.7, 18.8, 18.1, 17.7, −3.4, −3.5; IR (neat): 3310 (w), 2957 (m), 2930 (m), 2857 (m), 1472 (m), 1462 (m), 1384 (w), 1252 (m), 1182 (w), 1119 (m), 1086 (m), 1049 (s), 972 (w), 939 (w), 834 (s), 797 (m), 771 (s), 671 (m); HRMS-(ESI$^+$) for $C_{16}H_{35}O_2Si$ [M+H]: calculated: 287.2406, found: 287.2400. The crude reaction mixture was purified by silica gel chromatography (2:1 hexanes:diethyl ether) to afford a clear, colorless oil (67.0 mg, 98%, 10:1 dr). R_f = 0.51 (1:1 hexanes:ethyl acetate, stain in PMA).

[54] O'Neil, G. W.; Miller, M. M.; Carter, K. P. *Org. Lett*. **2010**, *12*, 5350.

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to the known compound[55] by ozonolysis/reduction.

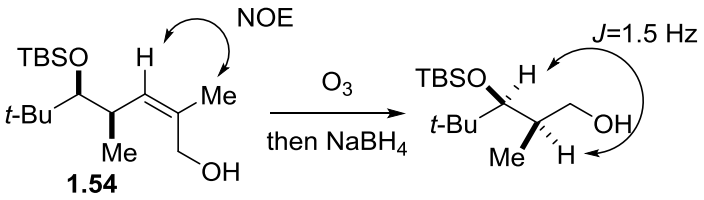


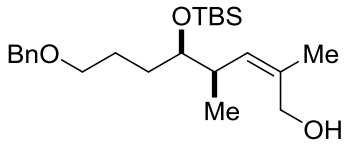


***syn*-(*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-2,4,6,6-tetramethylhept-2-en-1-ol (Table 1.2, entry 3).** The reaction was performed with the representative procedure but ran for 12 h at rt. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.34 (1H, d, *J* = 10.0 Hz), 4.14 (1H, d, *J* = 12.0 Hz), 4.11 (1H, d, *J* = 12.0 Hz), 3.19 (1H, d, *J* = 2.0 Hz), 2.76 (1H, ddq, *J* = 10.0 Hz, 6.5 Hz, 2.0 Hz), 1.78 (3H, d, *J* = 1.5 Hz), 1.3 (1H, br, s), 0.95-0.92 (12H, m), 0.89 (9H, s), 0.08 (3H, s), 0.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 131.3, 83.8, 61.8, 37.2, 33.9, 27.4, 26.6, 21.5, 19.0, 17.0, -2.6, -3.8; IR (neat): 3314 (br, w), 2955 (s), 2930 (s), 2857 (s), 1472 (m), 1252 (s), 1096 (s), 1026 (s), 876 (s), 770 (s); HRMS-(ESI$^+$) for $C_{17}H_{37}O_2Si$ [M+H]: calculated: 301.2563, found: 301.2552. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (57.0 mg, 89%, 7:1 dr). R_f = 0.35 (10:1 hexanes:ethyl acetate, stain in PMA).

[55] Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem*. **2001**, *66*, 894.

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by analyzing the chemical shift (3.51 ppm in $CDCl_3$) and *J*-value (1.5 Hz) between H_3 and H_2 of the diol shown below synthesized by ozonolysis/reduction.[56]



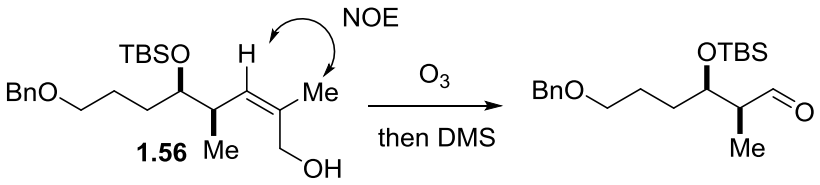


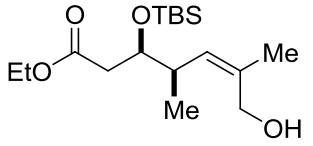
syn-(_Z_)-8-(benzyloxy)-5-((_tert_-butyldimethylsilyl)oxy)-2,4-dimethyloct-2-en-1-ol (Table 1.2, entry 4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.25 (5H, m), 5.06 (1H, d, *J* = 10.0 Hz), 4.50 (1H, d, *J* = 12.0 Hz), 4.47 (1H, d, *J* = 12.0 Hz), 4.25 (1H, dd, *J* = 12.0 Hz, 4.0 Hz), 3.87 (1H, dd, *J* = 11.5 Hz, 8.0 Hz), 3.57 (1H, ddd, *J* = 9.0 Hz, 5.0 Hz, 5.0 Hz), 3.49-3.46 (1H, m), 3.37-3.33 (1H, m), 2.60 (1H, qdd, *J* = 10.5 Hz, 6.5 Hz, 6.5 Hz), 2.16 (1H, dd, *J* = 4.0 Hz, 4.0 Hz), 1.77 (3H, s), 1.64-1.62 (3H, m), 1.49-1.43 (1H, m), 0.94 (3H, d, *J* = 6.5Hz), 0.89 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 134.6, 131.7, 128.6, 128.0, 127.8, 76.3, 73.2, 70.6, 61.8, 37.2, 31.3. 26.2, 24.8, 21.8, 18.5, 18.0, −4.1, −4.3; IR (neat): 3395 (m), 1968 (m), 2929 (m), 2870 (m), 1452 (m), 1474 (m), 1203 (w), 1094 (s), 1064 (s), 1005 (s), 947 (w), 929 (w), 865 (w), 735 (s), 697 (s), 610 (w); HRMS-(ESI$^+$) for $C_{23}H_{41}O_3Si$ [M+H]: calculated: 393.2825, found: 393.2813. The crude reaction mixture was purified by silica gel chromatography (6:1 hexanes:diethyl ether) to afford a clear, colorless oil (41.0 mg, 88%, >20:1 dr). R_f = 0.51 (3:1 hexanes:ethyl acetate, stain in

[56] Denmark, S. E.; Ghosh, S. K. *Angew. Chem. Int. Ed*. **2001**, *40*, 4759.

PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to known compound[57] by ozonolysis/reduction.



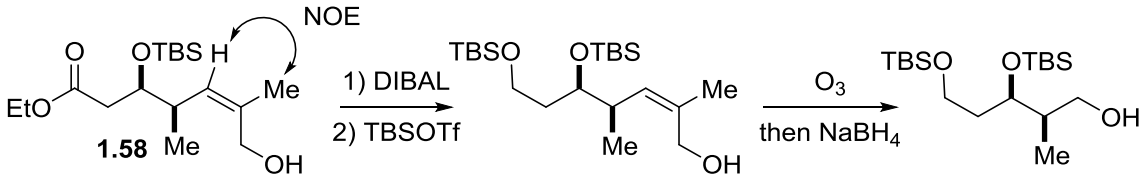


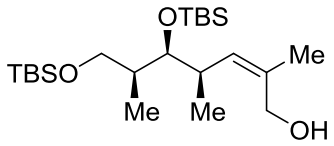
syn-(_Z_)-Ethyl-3-((_tert_-butyldimethylsilyl)oxy)-7-hydroxy-4,6-dimethylhept-5-enoate (Table 1.2, entry 5). The reaction was performed with the representative procedure but oxidized with pH=7 buffer instead of 3 M NaOH. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.04 (1H, d, *J* = 11.5 Hz), 4.28 (1H, d, *J* = 11.5 Hz), 4.10 (2H, dq, *J* = 8.5Hz, 7.5 Hz), 3.88 (1H, d, *J* = 12.0 Hz), 3.83 (1H, td, *J* = 5.5 Hz, 5.5 Hz), 2.70 (1H, qdd, *J* = 10.5 Hz, 7.0 Hz, 7.0 Hz), 2.46 (2H, d, *J* = 5.5 Hz), 1.79 (3H, s), 1.25 (3H, t, *J* =7.5 Hz), 0.96 (3H, d, *J* = 6.5 Hz), 0.88 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.4, 135.8, 130.9, 73.9, 61.9, 60.8, 41.1, 38.6, 26.0, 22.1, 18.3, 17.8, 14.3, −4.4, −4.5; IR (neat): 2957 (m), 2930 (m), 2857 (m), 1725 (s), 1472 (w), 1462 (w), 1374 (m), 1252 (s), 1175 (m), 1070 (s), 1006 (s), 940 (m), 832 (s), 774 (s), 666 (w); HRMS-(ESI$^+$) for $C_{17}H_{35}O_4Si$ [M+H]: calculated: 331.2305, found: 331.2292. The crude reaction mixture was purified by silica gel chromatography

[57] Danishefsky, S. J. Bertinato, P.; Dai-Shi, S.; Fang, M.; Ting-Chao, C.; Kamenecka, T.; Sorensen, E. J.; Balog, A.; Savin, K. A. *U.S. Patent 6*,369,234, **2002**.

(3:1 hexanes:diethyl ether) to afford a clear, colorless oil (27.0 mg, 80%, >20:1 dr). R_f = 0.57 (3:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to the known compound[12] shown below.

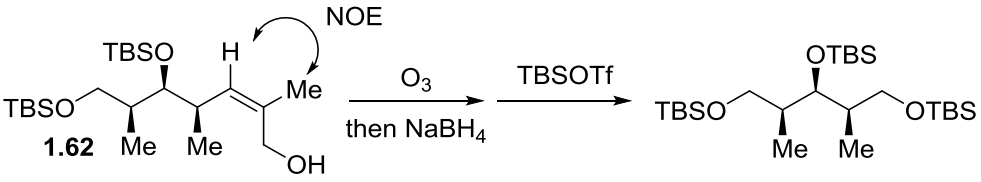


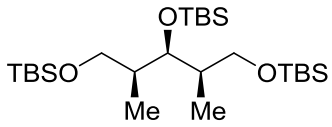


(4*R*,5*S*,6*S*,*Z*)-5,7-Bis((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylhept-2-en-1-ol (Table 1.2, entry 8). The reaction was performed with the representative procedure but at 0 °C for 12 h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.06 (1H, d, *J* = 10.0 Hz), 4.12 (1H, d, *J* = 11.5 Hz), 3.60 (1H, dd, *J* = 7.0 Hz, 2.5 Hz), 3.41 (1H, dd, *J* = 10.0 Hz, 8.0 Hz), 3.35 (1H, dd, *J* = 10.0 Hz), 2.58 (1H, dqd, *J* = 10.0 Hz, 7.0 Hz, 7.0 Hz), 1.77, (3H, s), 1.71 (1H, dq, *J* = 7.0 Hz, 2.0 Hz), 0.94 (3H, d, *J* = 6.5 Hz), 0.89 (9H, s), 0.87 (9H, s), 0.75 (3H, d, *J* = 7.0 Hz), 0.05 (3H, s), 0.04 (3H, s), 0.02 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.7, 132.8, 75.8, 66.0, 62.1, 39.3, 37.3, 26.5, 26.4, 21.8, 19.0, 18.8, 18.4, 10.8, −3.4, −3.8, −5.0, −5.1; IR (neat): 3345 (w), 2928 (s), 2980 (s), 2857 (s), 1472 (w), 1253 (s), 1089 (s), 835 (s), 774 (s). HRMS-(ESI$^+$) for $C_{22}H_{49}O_3Si_2$ [M+H]: calculated: 417.3220, found: 417.3211. $[\alpha]_D^{22}$ = +10.0 (c = 1.0, $CHCl_3$, l = 50 mm). The crude reaction mixture was

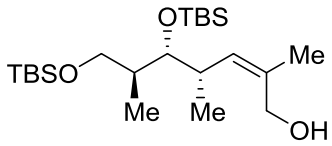
purified on silica gel (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (57.8 mg, 92%, 6:1 dr). R_f = 0.40 (10:1 hexanes:ethyl acetate, stain in PMA).

Proof of Stereochemistry: (*Z*)-alkene stereochemistry proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by ozonolysis/reduction/protection to furnish the symmetrical compound as determined by ^{1}H and ^{13}C NMR.

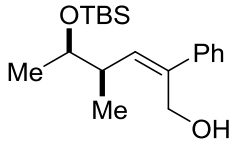




(6*R*,7*r*,8*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-2,2,3,3,6,8,11,11,12,12-decamethyl-4,10-dioxa-3,11-disilatridecane. Representative ^{1}H and ^{13}C NMR signals: ^{1}H NMR (500 MHz, C_6D_6): δ 3.75 (1H, dd, *J* = 3.5 Hz, 3.5 Hz), 3.52 (2H, dd, *J* = 9.5 Hz, 6.0 Hz), 3.35 (2H, dd, *J* = 9.5 Hz, 7.0 Hz), 1.76 (2H, m), 0.89 (27H, s), 0.86 (3H, d, *J* = 7.0 Hz), 0.04-0.03 (18H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 72.8, 66.1, 40.5, 26.4, 18.7, 18.5, 12.8, −3.8, −5.1, −5.1.

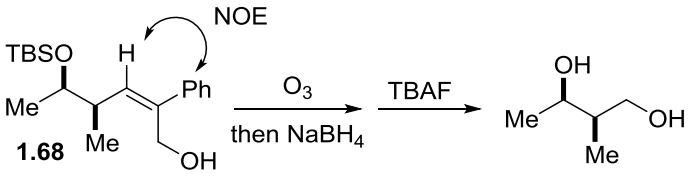


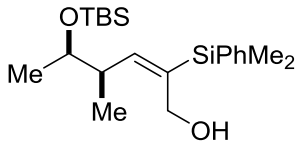
(4*S*,5*R*,6*S*,*Z*)-5,7-Bis((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylhept-2-en-1-ol. (Table 1.2, entry 9). For full characteristic data see Chapter 2.



***syn*-(*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-methyl-2-phenylhex-2-en-1-ol (Table 1.3, entry 3).** The reaction was performed with the representative procedure but at rt for 12 h. ^{1}H NMR (500 MHz, C_6D_6): δ 7.52 (2H, dd, *J* = 7.0 Hz, 1.0 Hz), 7.20 (2H, dd, *J* = 7.5 Hz, 7.5 Hz), 7.11 (1H, ddt, *J* = 7.5 Hz, 7.5 Hz, 1.0 Hz), 5.62 (1H, d, *J* = 10.5 Hz), 4.43 (1H, d, *J* = 12.0 Hz), 4.35 (1H, d, *J* = 12.0 Hz), 3.59 (1H, dq, *J* = 11.5 Hz, 5.0 Hz), 2.68 (1H, ddq, *J* = 10.0 Hz, 6.5 Hz, 5.0 Hz), 1.82 (1H, br s), 1.01 (3H, d, *J* = 6.0 Hz), 0.98 (9H, s), 0.07 (3H, s), 0.06 (3H, s); ^{13}C NMR (100 MHz, C_6D_6): δ 142.8, 141.0, 134.7, 129.0, 127.6, 127.2, 73.6, 60.7, 41.2, 26.5, 21.0, 18.9, 18.2, −3.9, −4.3; IR (neat): 3383 (br, w), 2957 (s), 2856 (m), 1462 (m), 1253 (s), 1094 (s), 1005 (s), 834 (s), 772 (s); HRMS-(ESI$^+$) for $C_{19}H_{33}O_2Si$ [M+H]: calculated: 321.2250, found: 321.2249. The crude reaction mixture was purified on silica gel (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (59.0 mg, 93%, 9:1 dr). R_f = 0.38 (10:1 hexanes:ethyl acetate, stain in PMA).

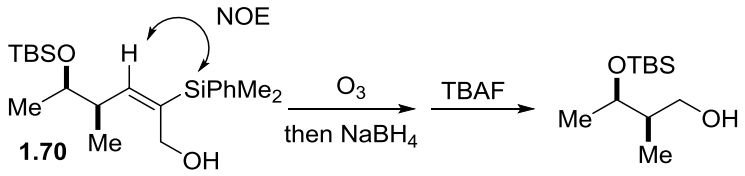
Proof of Stereochemistry: (*Z*)-alkene stereochemistry proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to the known diol[52] by ozonolysis/reduction/deprotection as shown below.





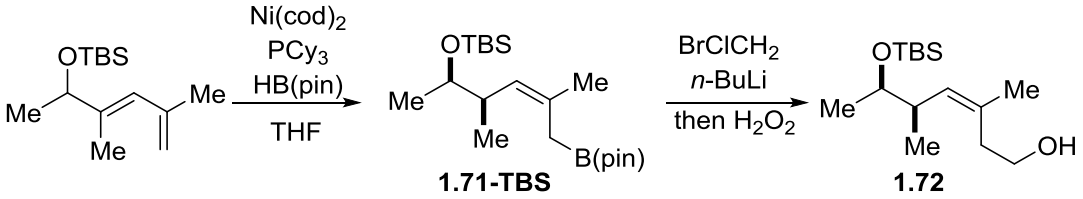
***syn*-(*Z*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-(dimethyl(phenyl)silyl)-4-methylhex-2-en-1-ol (Table 1.3, entry 4).** The reaction was performed with the representative procedure but with 40 mg of diene, and was heated to 40 °C for 12 h. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.53 (2H, m), 7.36-7.34 (3H, m), 5.76 (1H, d, *J* = 9.6 Hz), 4.27 (1H, dd, *J* = 12.0 Hz, 3.0 Hz), 4.18 (1H, dd, *J* = 12.0 Hz, 6.8 Hz), 3.68 (1H, dq, *J* = 6.4 Hz, 6.0 Hz), 2.70 (1H, ddq, *J* = 9.6 Hz, 6.8 Hz, 6.0 Hz), 1.69 (1H, dd, *J* = 4.8 Hz, 4.8 Hz), 1.06 (3H, d, *J* = 6.0 Hz), 0.97 (3H, d, *J* = 6.8 Hz), 0.90 (9H, s), 0.40 (3H, s), 0.40 (3H, s), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3, 139.5, 139.1, 134.2, 129.1, 128.0, 72.7, 60.7, 40.7, 26.1, 20.6, 18.5, 17.3, −2.3, −2.3, −4.2, −4.5; IR (neat): 3422 (br, w), 2955 (s), 2928 (s), 2855 (s), 1462 (m), 1250 (s), 1111 (s), 1026 (s), 834 (s), 773 (s); HRMS-(ESI^+) for $C_{21}H_{39}O_2Si_2$ [M+H]: calculated: 379.2489, found: 379.2476. The crude reaction mixture was purified on silica gel (15:1 hexanes:ethyl acetate) to afford a clear, colorless oil (36.0 mg, 84%, ≥ 10:1 dr). R_f = 0.29 (15:1 hexanes:ethyl acetate, stain in $KMnO_4$). The product contained two impurities in the crude ^{1}H NMR, both in less than 10%, that could not be separated.

Proof of Stereochemistry: (*Z*)-alkene stereochemistry was proven by NOE correlation as shown below. *Syn*-stereochemistry was proven by converting to the known diol[58] by ozonolysis/reduction as shown below.



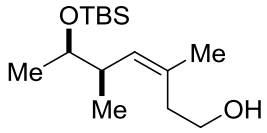
[58] Phukan, P.; Sasmal, S.; Maier, M. E. *Eur. J. Org. Chem*. **2003**, *68*, 1733.

III. Procedure for Hydroboration/Matteson Homologation (1.72, Scheme 1.18)



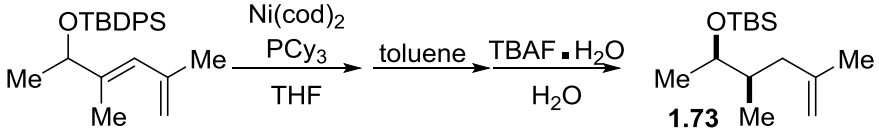
In the dry-box, an oven-dried 6-dram vial containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (0.20 mL of a 31.30 μM solution of $Ni(cod)_2$ in THF, 6.20 μmol), PCy_3 (0.2 mL of a 31.3 0 μM solution of PCy_3 in THF, 6.2 μmol), THF (1.00 mL, 0.25M), pinacolborane (33.5 mg, 0.26 mmol), and (*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (60 mg, 0.25 mmol). The vial was sealed with a polypropylene cap, removed from the dry-box, immediately cooled to 0 °C (ice/water), and allowed to stir for 3 h. The cap was then exchanged for a septum, and the vial was flushed with nitrogen. To the vial was added THF (1.5 mL) and bromochloromethane (18.4 μL, 0.27 mmol), at which point the vial was cooled to −78 °C (dry ice/acetone). Freshly titrated *n*-BuLi (0.12 mL of a 2.3 M solution in hexane, 0.27 mmol) was added dropwise, and the reaction was allowed to stir at −78 °C for 10 min. The reaction was then allowed to warm to room temperature and stir for 16 h. The reaction mixture was cooled to 0 °C and charged with 3 M sodium hydroxide (1 mL) and 30% hydrogen peroxide (0.75 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (1 mL) was added dropwise. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude

reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (61.2 mg, 90%, 14:1 dr).



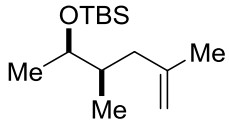
syn-(_Z_)-6-((_tert_-Butyldimethylsilyl)oxy)-3,5-dimethylhept-3-en-1-ol (Scheme 1.18, 1.72). ^{1}H NMR (500 MHz, C_6D_6): δ 5.21 (1H, d, *J* = 9.5 Hz), 3.62 (1H, dq, *J* = 6.0 Hz, 4.5 Hz), 3.58 (2H, m), 2.54 (1H, dqd, *J* = 10.0 Hz, 7.0 Hz, 6.5 Hz), 2.27 (2H, m), 1.73 (3H, s), 1.19 (3H, d, *J* = 6.0 Hz), 1.12-1.08 (12H, m), 0.19 (3H, s), 0.18 (3H, s); ^{13}C NMR (100 MHz, C_6D_6): δ 132.2, 131.9, 73.8, 61.2, 41.2, 36.4, 26.7, 24.3, 22.4, 19.0, 18.2, −3.6, −4.1; IR (neat): 3328 (br, w), 2957 (s), 2929 (s), 2857 (s), 1472 (m), 1448 (m), 1254 (s), 1122 (s), 1050 (s), 835 (s), 807 (s); HRMS-(ESI$^+$) for $C_{15}H_{33}O_2Si$ [M+H]: calculated: 273.2250, found: 273.2237. The crude reaction mixture was purified by silica gel chromatography (10:1 hexanes:ethyl acetate) to afford a clear, colorless oil (61.2 mg, 90%, 14:1 dr). R_f = 0.30 (10:1 hexanes:ethyl acetate, stain in PMA).

IV. Procedure for Hydroboration/Protodeboration (1.73, Scheme 1.18)



In the dry-box, an oven-dried 6-dram vial containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (0.1 mL of 1.3 μM solution of $Ni(cod)_2$ in THF, 0.13 μmol), PCy_3 (0.1 mL of 1.3 μM solution of PCy_3 in THF, 0.13 μmol), THF (0.05 mL), pinacolborane (7.7 mg, 0.06 mmol), and (*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)diphenylsilane (20.0 mg, 0.055 mmol). The vial was sealed with a polypropylene

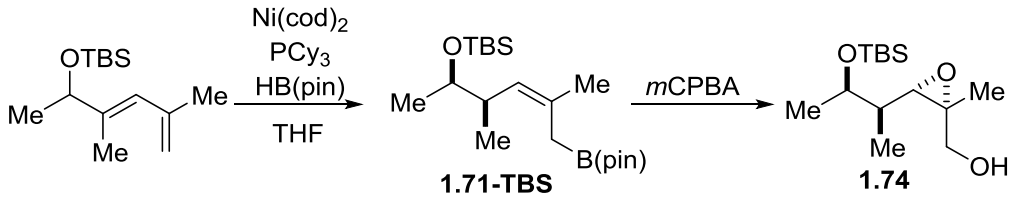
cap, removed from the dry-box, and allowed to stir at room temperature for 24 h. The solvent was then removed by rotary evaporation, and TBAF·nH_2O (26 mg, 0.11 mmol) was added. The vial was capped with a septum and purged with nitrogen. Toluene (1.2 mL) was then added, followed by deionized water (2.0 μL). The septum was quickly exchanged for a polypropylene cap, and the reaction was allowed to stir at 60 °C for 6 h. The reaction was diluted with diethyl ether and run through a silica pipet column eluting with diethyl ether, followed by concentration by rotary evaporation. The crude material was purified by silica gel chromatography (40:1 hexanes:diethyl ether) to afford the title compound as a clear, colorless oil (17.0 mg, 83%). R_f = 0.84 (20:1 hexanes:diethyl ether, stain with $KMnO_4$).



***syn-tert*-Butyl((3,5-dimethylhex-5-en-2-yl)oxy)diphenylsilane (Scheme 1.18, 1.73).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71-7.68 (4H, m), 7.44-7.40 (2H, m), 7.37 (4H, t, *J* = 7.0 Hz), 4.72 (1H, s), 4.63 (1H, s), 3.83 (1H, qd *J* = 6.0 Hz, 3.0 Hz), 2.34 (1H, dd, *J* = 13.0 Hz, 4.0 Hz), 1.83 (1H, dd, *J* = 13.5 Hz, 10.0 Hz), 1.71-1.68 (1H, m), 1.66 (3H, s), 1.06 (9H, s), 0.97 (3H, d, *J* = 6.0 Hz), 0.77 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 136.2, 136.1, 135.3, 134.6, 129.7, 129.6, 127.7, 127.5, 111.5, 73.0, 40.4, 37.9, 27.3, 22.4, 19.6, 19.4, 14.6; IR (neat): 3071 (w), 2964 (m), 2932 (m), 2858 (m), 1472 (w), 1427 (m), 1380 (m), 1362 (m), 1146 (w), 1106 (s), 1083 (s), 1043 (s), 956 (w), 888 (w), 765 (m), 701 (s); HRMS-(ESI^+) for $C_{24}H_{35}OSi$ [M+H]: calculated: 367.2457, found: 367.2475. The crude reaction mixture was purified by silica gel chromatography (20:1 hexanes:diethyl ether) to afford a clear,

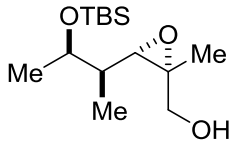
colorless oil (17.0 mg, 83%, >20:1 dr). R_f = 0.84 (20:1 hexanes: diethyl ether, stain in $KMnO_4$).

V. Procedure for Hydroboration/Epoxidation (1.74, Scheme 1.18)



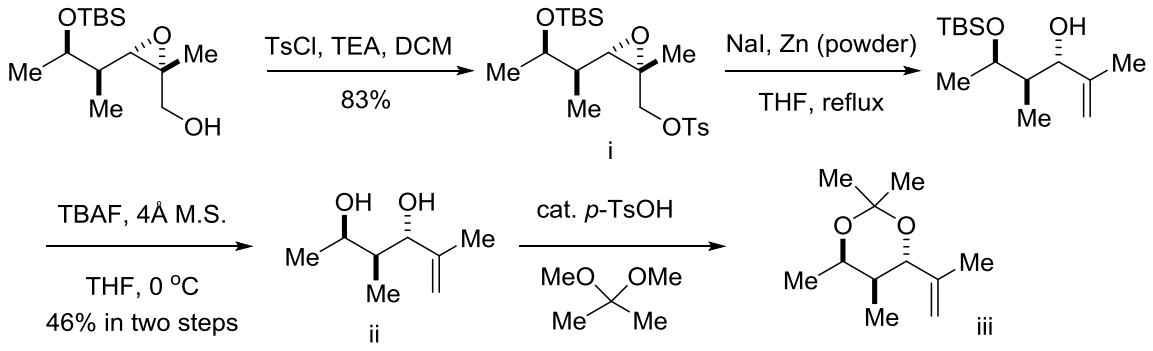
In the dry-box, an oven-dried 6-dram vial containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (1.9 mg, 6.80 μmol), PCy_3 (1.9mg, 6.80 μmol), THF (1.08 mL, 0.25M), pinacolborane (35.8 mg, 0.28 mmol), and (*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)dimethylsilane (64 mg, 0.27 mmol). The vial was sealed with a polypropylene cap, removed from the dry-box, and allowed to stir at 0 °C for 3 h. The solvent was then removed by rotary evaporation, and K_2HPO_4 (268 mg, 1.08 mmol) was added. The flask was purged with N_2 and CH_2Cl_2 (0.7 mL) and MeOH (86 μL, 2.16 mmol, distilled) were then added, and the flask was cooled to 0 °C. A solution of *m*CPBA (266.0 mg, 70%, 1.08 mmol) in CH_2Cl_2 (2 mL) was added dropwise at 0 °C and the reaction mixture was allowed to stir at 0 °C for 3 h. The crude reaction mixture was quenched with saturated Na_2CO_3 (2.0 mL), diluted with ethyl acetate (5 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 5 mL) and the combined organic layers were washed with saturated Na_2CO_3, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (4:1 hexanes:diethyl ether) to afford the title compound **1.74** as a clear, colorless oil (53.5 mg, 72%, 7:1 dr). R_f = 0.36 (4:1 hexanes:ethyl acetate, stain with

PMA).

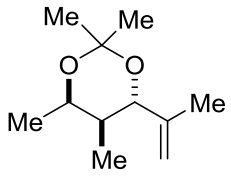


(3-3-((*tert*-Butyldimethylsilyl)oxy)butan-2-yl)-2-methyloxiran-2-yl)methanol (Scheme 1.18, 1.74). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.93 (1H, qd, *J* = 6.0 Hz, 4.5 Hz), 3.92 (1H, quin, *J* = 6.5 Hz), 3.70 (1H, dd, *J* = 11.5 Hz, 7.0 Hz), 3.65 (1H, dd, *J* = 12.0 Hz, 5.0 Hz), 2.75 (1H, d, *J* = 9.5 Hz), 1.40 (3H, s), 1.40-1.35 (1H, m), 1.16 (3H, d, *J* = 6.0 Hz), 0.93 (3H, d, *J* = 6.0 Hz), 0.90 (9H, s), 0.07 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 69.7, 67.4, 64.2, 60.9, 40.0, 26.1, 22.1, 20.7, 18.3, 10.9, −4.0, −4.8; IR (neat): 3446 (w), 2956 (m), 2930 (m), 2857 (m), 1726 (w), 1472 (m), 1462 (m), 1253 (s), 1149 (m), 1117 (m), 1070 (s), 1023 (s), 960 (s), 892 (m), 835 (s), 801 (s), 773 (s), 707 (m); HRMS-(ESI$^+$) for $C_{14}H_{30}O_3Si$ [M+H]: calculated: 275.2043, found: 275.2052.

Proof of Stereochemistry: The relative configuration was assigned by comparison of the ^{13}C NMR spectrum according to literature reports,[59] after conversion of **1.74** into acetonide **iii**, as shown below.

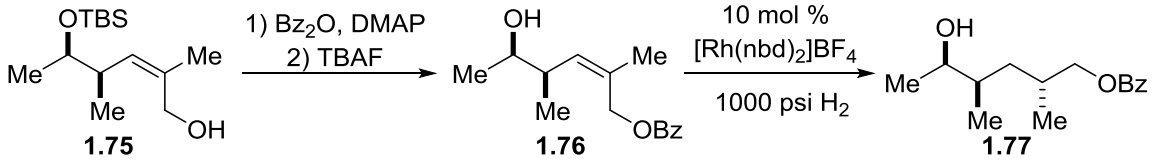


[59] Bestmann, H. J.; Liepold, B.; Kress, A.; Hofmann, A. *Chem. Eur. J.* **1999**, *5*, 2984.

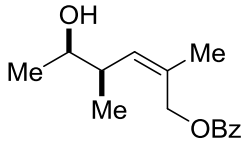


2,2-Dimethoxy-4,5-dimethyl-6-(prop-1-en-2-yl)-1,3-dioxane ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (1H, q, *J* = 1.0 Hz), 4.87 (1H, q, *J* = 1.5Hz), 4.09 (1H, qd, *J* = 6.5 Hz, 5.0 Hz), 3.72 (1H, d, *J* = 8.5 Hz), 1.85 (1H, m), 1.77 (3H, s), 1.38 (3H, s), 1.37 (3H, s), 1.11 (3H, d, *J* = 6.5 Hz), 0.84 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 112.6, 100.6, 78.9, 65.5, 37.9, 25.5, 24.4, 18.2, 17.0, 11.9; IR (neat): 2955 (s), 2926 (s), 2863 (s), 1737 (w), 1651 (w), 1622 (w), 1446 (m), 1377 (m), 1225 (m), 1143 (m), 1093 (m), 1022 (m), 895 (w), 861 (w), 817 (w).

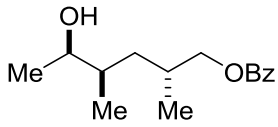
VI. Procedure for Diastereoselective Hydrogenation (Scheme 1.19)



In the dry-box, an oven-dried 1-dram vial containing a stir bar was charged with (*Z*)-5-hydroxy-2,4-dimethylhex-2-en-1-yl benzoate **1.76** (20 mg, 0.08 mmol), [Rh(nbd)dppb]BF_4 (5.6mg, 0.008 mmol), and CH_2Cl_2 (152 μL). The vial was removed from the box and the mixture was stirred under 1000 psi of H_2 gas in a hydrogen bomb for 2 h. The resulting solution was filtered through a short plug of silica gel, washing with diethyl ether. The solution was concentrated by rotary evaporation to afford the title compound as a clear, colorless oil (18.5 mg, 92%, 7:1 dr). R_f = 0.43 (4:1 hexanes: ethyl acetate, stain in PMA).

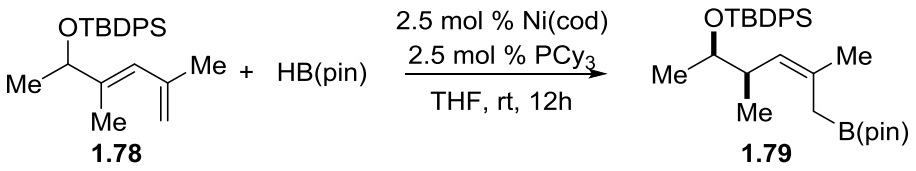


***syn-(Z)*-5-Hydroxy-2,4-dimethylhex-2-en-1-yl benzoate (Scheme 1.19, 1.76).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (2H, d, *J* = 7.5 Hz), 7.56 (1H, t, *J* = 7.5 Hz), 7.44 (2H, t, *J* = 7.0 Hz), 5.32 (1H, d, *J* = 10.0 Hz), 4.92 (1H, d, *J* = 12.0 Hz), 4.82 (1H, d, *J* = 12.0 Hz), 3.67 (1H, qd, *J* = 6.0 Hz, 6.0 Hz), 2.68 (1H, qdd, *J* = 10.0 Hz, 6.0 Hz, 6.0 Hz), 1.86 (3H, s), 1.15 (3H, d, *J* = 6.5 Hz), 1.02 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 133.2, 132.8, 131.2, 130.4, 129.8, 128.6, 71.9, 64.2, 39.8, 22.0, 20.1, 17.2; IR (neat): 3411 (w), 2968 (m), 2930 (w), 2847 (w), 1717 (s), 1601 (w), 1492 (w), 1451 (m), 1378 (m), 1314 (m), 1266 (s), 1176 (m), 1108 (s), 1025 (s), 902 (m), 709 (s); HRMS-(ESI$^+$) for $C_{15}H_{21}O_3$ [M+H]: calculated: 249.1491, found: 249.1498. The crude reaction mixture was purified by silica gel chromatography (5:1 hexanes:diethyl ether) to afford a clear, colorless oil (78.0 mg, 81%). R_f = 0.28 (5:1 hexanes: ethyl acetate, stain in PMA).

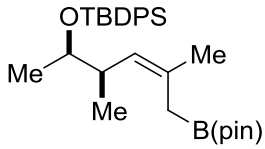


5-Hydroxy-2,4-dimethylhexyl benzoate (Scheme 1.19, 1.77). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (2H, d, *J* = 8.5 Hz), 7.56 (1H, t, *J* = 2.5 Hz), 7.44 (2H, t, *J* = 2.5 Hz), 4.20 (1H, dd, *J* = 10.5 Hz, 6.0 Hz), 4.12 (1H, dd, *J* = 10.5 Hz, 6.5 Hz), 3.73 (1H, qd, *J* = 6.0 Hz, 4.5 Hz), 2.07-2.00 (1H, m), 1.67-1.58 (1H, m), 1.32 (2H, ddd, *J* = 8.5 Hz, 5.0 Hz, 3.0Hz), 1.17 (3H, d, *J* = 6.5 Hz), 1.01 (3H, d, *J* = 6.0 Hz), 0.90 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 133.1, 130.6, 129.7, 128.6, 71.9, 70.7, 37.0, 36.4, 30.5, 20.4, 16.7, 14.2; IR (neat): 3473 (w), 2966 (m), 2931 (w), 1718 (s), 1379 (w), 1314 (m), 1272 (s), 1113 (s), 1070 (m), 1026 (w), 711 (s), 678 (w), 675 (w); HRMS-(ESI$^+$) for $C_{15}H_{23}O_3$ [M+H]: calculated: 251.1647, found: 251.1644.

VII. Procedure for One gram Hydroboration (Scheme 1.20)



In the dry-box, a flame-dried 50 mL round-bottom flask containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (19.3 mg, 0.070 mmol), PCy_3 (19.6 mg, 0.070 mmol), THF (11.2 mL, 0.25M), pinacolborane (0.43 mL, 2.94 mmol), and (*E*)-*tert*-butyl((3,5-dimethylhexa-3,5-dien-2-yl)oxy)diphenylsilane **1.78** (1.02 g, 2.80 mmol). The flask was capped with a septum, removed from the dry-box, and allowed to stir for 24 h at rt. The solvent was then removed by rotary evaporation and the crude reaction mixture was purified by silica gel chromatography (100:1 hexanes:ethyl acetate) to afford the title compound as a clear, light yellow oil (1.01 g, 74% (93% brsm), >20:1 dr). R_f = 0.29 (100:1 hexanes:ethyl acetate, stain with $KMnO_4$).



***tert*-Butyl((*syn*-*Z*)-3,5-dimethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hex-4-en-2-yl)oxy)diphenylsilane (Scheme 1.20, 1.79).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73-7.35 (4H, m), 7.43-7.35 (6H, m), 5.00 (1H, dd, *J* = 9.5 Hz, 1.0 Hz), 3.68 (1H, dq, *J* = 6.5 Hz, 6.5 Hz), 2.34 (1H, ddq, *J* = 10.0 Hz, 6.5 Hz, 6.5 Hz), 1.71 (1H, d, *J* = 15.0 Hz), 1.56 (1H, d, *J* = 15.0 Hz), 1.21 (12H, s), 1.05 (9H, s), 1.00 (3H, d, *J* = 6.5 Hz), 0.95 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.2, 136.2, 135.6, 134.7, 131.3, 129.5, 129.4, 127.8, 127.6, 127.5, 83.3, 74.2, 41.1, 27.3, 26.1, 25.0, 24.9, 21.9, 19.7, 16.9; IR (neat): 3071 (w), 3048 (m), 2974 (m), 2891 (m), 1472 (s), 1371 (s), 1323 (s), 1143 (s), 1109 (s), 959 (m),

738 (m), 702 (s), 507 (m); HRMS-(ESI^+) for $C_{30}H_{45}O_3BSi$ [M+Na]: calculated: 515.3129, found: 515.3126.

Chapter 2

Total Synthesis of Discodermolide by Catalytic Stereoselective Borylation Reactions[1] And Progress toward Oxidation-Resistant Analog Synthesis

2.1 Introduction

Polyketides are a class of important natural products that often show potent biological activities and useful pharmacological properties (Chapter 1).[2] Indeed, approximately 20% of top selling small molecule drugs fall into the category of polyketides, and polyketides are about five times more likely to possess an active biological activity compared to other families of natural products.[2c,d] While most polyketides are derived from soil bacteria or marine sponges and might be considered to be readily available, it is estimated that less than 5% of the soil bacterial are amendable to culture and this number is even smaller for marine sponge.[3]

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[1] Yu, Z.; Ely, R. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 9632.

[2] (a) *Macrolide Antibiotics. Chemistry, Biology, and Practice*, 2nd ed.; Omura, S., Ed.; Academic Press: New York, 2002. (b) *Polyketides Biosynthesis, Biological Activity, and Genetic Engineering*; Rimando, A. M., Baerson, S. R., Eds.; ACS Symposium Series 955; American Chemical Society: Washington, DC, 2007. (c) Newman, D. J.; Cragg, G. M. *J. Nat. Prod*. **2007**, *70,* 461. (d) Newman, D. J.; Grothaus, P.G.; Cragg, G. M. *Chem. Rev***. 2009**, *109*, 3012. (e) O'Hagan, D. *The Polyketide Metabolites*; Ellis Horwood: Chichester,U.K., 1991.

[3] Sait, M.; Hugenholtz P.; Janssen, P. H.; *Environ. Microbiol.* **2002**, *4*, 654. and references cited therein.

Considering their importance in drug discovery, preparation and manufacture of polyketides has become an important topic. Fermentation and semi-syntheses have provided good routes to obtain large quantity of some polyketides, and these methods are responsible for nearly all the polyketides on market.[4] However it is hard to apply these two methods to polyketides with low isolation yield and limited natural sources. Under such circumstances, chemical synthesis serves as an important and powerful tool to construct the polyketide structure. Thus, it is of great importance to develop novel and reliable methods to construct polyketides concisely and rapidly.

One example of such molecule is (+)-discodermolide, a polyketide isolated from sea sponge *discodermia dissoluta* and the most potent microtubule stabilizer yet discovered.[5] Neither fermentation nor semi-synthesis is applicable to obtain large quantity of discodermolide, because it has very low isolation yield from nature (0.002% *w/w*) and no responsible organism for its production has been identified. Chemical synthesis was the only way to obtain large quantity of discodermolide, and a number of efforts have been attracted toward its total synthesis. While some portions of the structure are easily assembled, stereocontrolled construction of the trisubstituted C13-C14 (*Z*)-

[4] A notable exception is eribulin which requires 33 steps (longest linear sequence) and 65 total steps: (a) Chase, C. E.; Fang, F. G.; Lewis, B. M.; Wilkie, G. D.; Schnaderbeck, M. J.; Zhu, X. *Synlett*, **2013**, 323. (b) Austad, B. C.; Benayoud, F.; Calkins, T. L.; Campagna, S.; Chase, C. E.; Choi, H.-W.; Christ, W.; Costanzo, R.; Cutter, J.; Endo, A.; Fang, F. G.; Hu, Y.; Lewis, B. M.; Lewis, M. D.; McKenna, S.; Noland, T. A.; Orr, J. D.; Pesant, M.; Schnaderbeck, M. J.; Wilkie, G. D.; Abe, T.; Asai, N.; Asai, Y.; Kayano, A.; Kimoto, Y.; Komatsu, Y.; Kubota, M.; Kuroda, H.; Mizuno, M.; Nakamura, T.; Omae, T.; Ozeki, N.; Suzuki, T.; Takigawa, T.; Watanabe, T.; Yoshizawa, K. *Synlett,* **2013**, 327 (c) Austad, B. C.; Calkins, T. L.; Chase, C. E.; Fang, F. G.; Horstmann, T. E.; Hu, Y.; Lewis, B. M.; Niu, X.; Noland, T. A.; Orr, J. D.; Schaderbeck, M. J.; Zhang, H.; Asakawa, N.; Asai, N.; Chiba, H.; Hasebe, T.; Hoshino, Y.; Ishizuka, H.; Kajima, T.; Kayano, A.; Komatsu, Y.; Kubota, M.; Kuroda, H.; Miyazawa, M.; Tagami, K.; Watanabe, T. *Synlett*, **2013**, 333.

[5] Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem*. **1990**, *55*, 4912. Correction: *J. Org. Chem*. **1991**, *56*, 1346.

olefin[6] still remains a challenging task in discodermolide syntheses. We suspected that Ni-catalyzed diastereoselective hydroboration (Chapter 1) could rapidly construct the core trisubstituted (*Z*)-olefin as well as the adjacent propionate moiety, rendering a short and efficient synthesis of (+)-discodermolide.

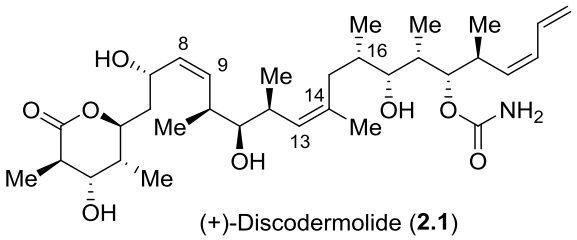
2.2 Background

2.2.1 Discovery and Biological Activity of (+)-Discodermolide

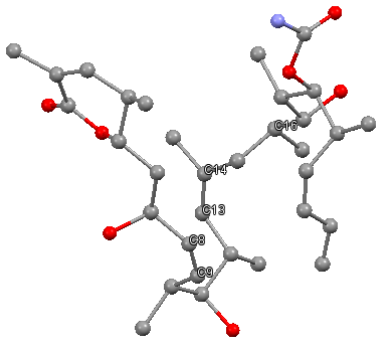
In 1990, (+)-discodermolide **2.1** was first isolated by Gunaskera and co-workers at the Harbor Branch Oceanographic Institute by a bio-assay guided fractionation of extracts from the deep sea marine sponge *Discodermia dissoluta.*[5] The structure was determined by employing a battery of NMR experiments, including ^{1}H, ^{13}C, COSY, long range COSY, and several 2D correlation experiments as well as X-ray crystallography. The structure was found to feature 13 stereogenic centres, a fully substituted δ-lactone, one C8-C9 disubstitued and one C13-C14 trisubstituted (*Z*)-alkene, a terminal (*Z*)-diene and a carbamate moiety (Figure 2.1). Discodermolide adopts a U-shaped conformation, where the internal (*Z*)-trisubstituted alkene locks the conformation such that A(1,3) strain is minimized as are *syn*-pentane interactions along the backbone (Figure 2.1, X-ray structure).

[6] For recent examples of stereocontrolled trisubstituted olefin synthesis, see; (a) Moure, A. L.; Arrayás, A. G.; Cárdenas, D. J.; Alonso, I.; Carretero, J. C. *J. Am. Chem. Soc*. **2012**, *134*, 7219. (b) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 419. (c) Rooke, D. A.; Ferreira, E. M. *J. Am. Chem. Soc*. **2010**, *132*, 11926. (d) Belardi, J. K.; Micalizio, G. C. *J. Am. Chem. Soc*. **2008**, *130*, 16870. (e) Xie, Q.; Denton, R. W.; Parker, K. A. *Org. Lett*. **2008**, *10*, 5345. (f) Prantz, K.; Mulzer, J. *Chem. Eur. J*. **2010**, *16*, 485.

Figure 2.1. (+)-Discodermolide and Its X-ray Structure



(+)-Discodermolide (**2.1**)



Compared to other microtubule stabilizing reagents, discodermolide is characteristically unique not only in its linear backbone structure but also in a number of biological activities. (+)-Discodermolide was initially identified as a highly immunosuppressive agent both in *vitro* [7] and in *vivo* [8], which was discovered by researchers at Harbor Branch during early biological evaluation. Further study demonstrated that discodermolide has antiproliferative activity which remarkably blocks the cell cycle at G_2/M phase.[9] Similar to paclitaxel,[10] (+)-discodermolide stabilizes tubulin,[11] but discodermolide mediated microtubule polymerization was faster than equimolar concentration of paclitaxel. As low as 10 μM concentration of discodermolide was able to promote microtubule polymerization even in the absence of GTP; however, paclitaxel was completely inactive under such conditions. It was also found that discodermolide-induced microtubules were more in number and grew shorter in length

[7] Longley, R. E.; Caddigan, D.; Harmony, D.; Gunasekera, M.; Gunasekera, S. *Transplantation* **1991**, *52*, 650.
[8] Longley, R. E.; Caddigan, D.; Harmony, D.; Gunasekera, M.; Gunasekera, S. *Transplantation* **1991**, *52*, 656.
[9] Longley, R. E.; Gunasekera, S. P.; Faherty, D.; McLane, J.; Dumont, F. Ann. *N.Y. Acad. Sci.* **1993**, *696*, 94.
[10] Parness, J., and Horwitz, S. B. *J. Cell Biol.* **1981,** *91*, 479.
[11] ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243.

than the ones induced by paclitaxel. Competitive microtubule-binding experiments between discodermolide and paclitaxel revealed that they bind in a mutually exclusive manner, implying the same or overlapping binding sites on microtubules.[12] Though a number of experiments were designed to find the precise discodermolide binding domain of tubulin, the binding mode and orientation still remain speculative.[13]

(+)-Discodermolide maintained cytotoxicity against taxol-resistant and multi-drug resistant cell lines. For example, SW620AD-300 colon carcinoma line displayed a 930-fold increased resistance to paclitaxel, while discodermolide was only 25-fold less potent in this cell line.[14] Further studies revealed the synergistic cytotoxicity of discodermolide/paclitaxel combination both in *vitro*[15] and in *vivo*.[16] Though the precise mechanism of the observed synergism remained unknown, it was speculated by Horwitz and Smith that the two agents might preferentially target different tubulin isotypes.[17]

The outstanding biological activities as well as challenging structures have rendered discodermolide a great target for total synthesis as a drug candidate. Notably, chemical synthesis became the sole method to obtain large quantity of discodermolide because of its low isolation yield (0.002% *w/w*) and no identifiable cultivated production

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[12] Hung, D. T.; Chen, J.; Schreiber, S. L. *Chem. Biol*. **1996**, *3*, 287.
[13] (a) Mattello, L. A.; LaMarche, M. J.; He, L.; Beauchamp, T. J.; Smith, A. B.; Horwita, S. B. *Chem. Biol.* **2001**, *8*, 843. (b) Monteagudo, E.; Cicero, D. O.; Cornett, B.; Myles, D. C.; Snyder, J. P. *J. Am. Chem. Soc*. **2001**, *123*, 6929. (c) Smith, A. B.; LaMarche, M. J.; Falcone-Hindley, M. *Org. Lett*. **2001**, *3*, 659. (d) Klein, L. E., Freeze, B. S., Smith, A. B.III, and Horwitz, S. B. *Cell Cycle* **2005**, *4*, 501. (e) Khrapunovich-Baine, M.; Menon, V.; Verdier-Pinard, P.; Smith, A. B. III, Angeletti, R. H.; Fiser, A.; Horwitz, S. B.; Xiao, H. *Biochemistry* **2009**, *48*, 11664.
[14] Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Pharmacol*. **1997**, *52*, 613.
[15] Martello, L. A.; McDaid, H. M.; Regl, D. L.; Yang, C.-P. H.; Meng, D.; Pettus, T. R. R.; Kaufman, M. D.; Arimoto, H.; Danishefsky, S. J.; Smith, A. B., III; Horwitz, S. B. *Clin. Cancer Res*. **2000**, *6*, 1978.
[16] Honore, S.; Kamath, K.; Braguer, D.; Horwitz, S. B.; Wilson, L.; Briand, C.; Jordan, M. A. *Cancer Res.* **2004**, *64*, 4957.
[17] Huang, G. S.; Lopez-Barcons, L.; Freeze, B. S.; Smith, A. B., III; Goldberg, G. L.; Horwitz, S. B.; McDaid, H. M. *Clin. Cancer Res*. **2006**, *12*, 298.

organism. Thus, it is not surprising that discodermolide became one of the most studied polyketide nature products. Indeed, there are 14 total syntheses of discodermolide from 10 different groups, both in academia and industry.[18] However, construction of C13-C14 (*Z*)-trisubstituted olefin and efficient fragment union still remained the most challenging problems for the synthesis. Most of previous approaches prepare discodermolide from three equally complex fragments for convergent syntheses. Some selected examples are briefly discussed below.

[18] For completed total syntheses of discodermolide, see; (a) Nerenberg, J. B.; Hung, D. T.; Somers, P. K.; Schreiber, S. L. *J. Am. Chem. Soc*. **1993**, *115*, 12621. (b) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *Chem. Biol*. **1994**, *1*, 67. (c) Smith, A. B., III; Qiu, Y.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12011. (d) Hung, D. T.; Nerenberg, J. B.; Schreiber, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 11054. (e) Harried, S. S.; Yang, G.; Strawn, M. A.; Myles, D. C. *J. Org. Chem*. **1997**, *62*, 6098. (f) Marshall, J. A.;Johns, B. A. *J. Org. Chem*. **1998**, *63*, 7885. (g) Smith, A. B., III; Kaufman, M. D.; Beauchamp, T. J.; LaMarche, M. J.; Arimoto, H. *Org. Lett*. **1999**, *1*, 1823. (h) Halstead, D. P. Ph.D. Thesis, Harvard University, Cambridge, MA, 1999. (i) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 377. (j) Harried, S. S.; Lee, C. P.; Yang, G.; Lee, T. I. H.; Myles, D. C. *J. Org. Chem*. **2003**, *68*, 6646. (k) Smith, A. B.; Freeze, B. S.; Brouard, I.; Hirose, T. *Org. Lett*. **2003**, *5*, 4405. (l) Paterson, I.; Delgado, O.; Florence, G. J.; Lyothier, I.; Scott, J. P.; Sereinig, N. *Org. Lett*. **2003**, *5*, 35. (m) Mickel, S. J.; Niederer, D.; Daeffler, R.; Osmani, A.; Kuesters, E.; Schmid, E.; Schaer, K.; Gamboni, R.; Chen, W.; Loeser, E.; Kinder, F. R., Jr.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Repic, O.; Wang, R.-M.; Florence, G.; Lyothier, I.; Paterson, I. *Org. Process Res. Dev*. **2004**, *8*, 122 and references cited therein. (n) Arefolov, A.; Panek, J. S. *J. Am. Chem. Soc*. **2005**, *127*, 5596. (o) Smith, A. B., III; Freeze, B. S.; Xian, M.; Hirose, T. *Org. Lett*. **2005**, *7*, 1825. (p) Paterson, I.; Lyothier, I. *Org. Lett*. **2004**, *6*, 4933. (q) de Lemos, E.; Porée, F.-H.; Commerçon, A.; Betzer, J.-F.; Pancrazi, A.; Ardisson, J. *Angew. Chem. Int. Ed*. **2007**, *46*, 1917. (r) see ref.1

2.2.2 Selected Examples of (+)-Discodermolide Syntheses and C13-C14 (*Z*)-Olefin Syntheses

The first total synthesis of the unnatural antipode (−)-discodermolide was completed by Schreiber and co-workers in 1993,[18a] and it proved the absolute stereochemistry and confirmed the relative stereochemistry of the natural product. Later, in 1996, they reported a full article for the synthesis of the natural antipode (+)-discodermolide (Scheme 2.1).[18d] Retrosynthetically, the molecule was disconnected to three fragments (**2.2**, **2.3**, and **2.4**). (*Z*)-Trisubstituted olefin **2.9** was constructed *via* Still-Gennari olefination[19] from aldehyde **2.6**, a compound that was prepared in 6 steps from commercially available Roche ester **2.5**; subsequent five-step transformation furnished alkynyl iodide **2.3** fragment. The key fragment unions include a Nozaki-Hiyama-Kishi coupling[20] of **2.2** and **2.3** to deliver adduct **2.10**, followed by partial hydrogenation to secure the C8-C9 *cis*-olefin and four more steps to afford allylbromide **2.11** as left-half of discodermolide. A lithium enolate, prepared by deprotection of methyl ketone **2.4**, displaced allylbromide **2.11** to build the C15-C16 bond and complete the discodermolide backbone. Then methylation at C15 position gave **2.12** with moderate (3:1) diatereoselectivity. Subsequent transformations including a directed ketone reduction and global deprotection completed the total synthesis of (+)-discodermolide with 24 longest linear sequence (36 total steps) in an overall yield of 4.3%.

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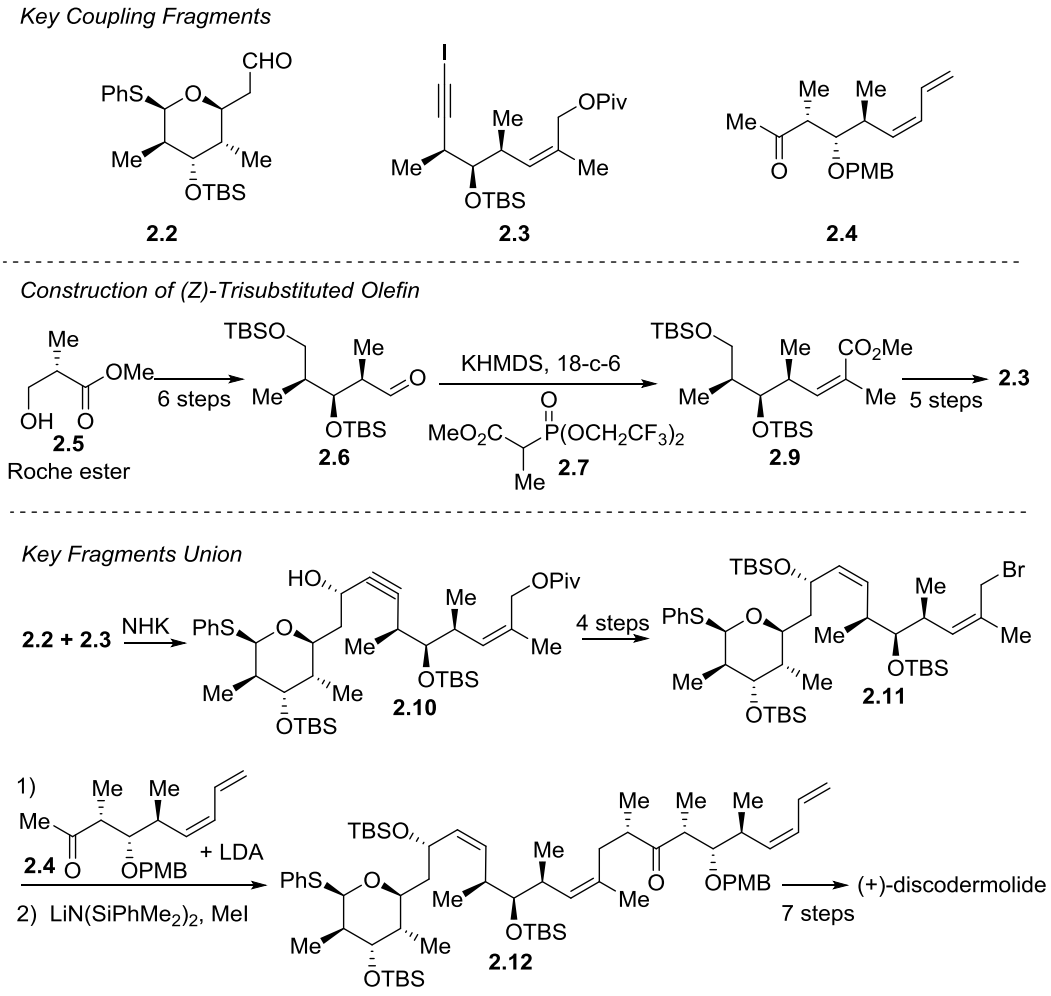
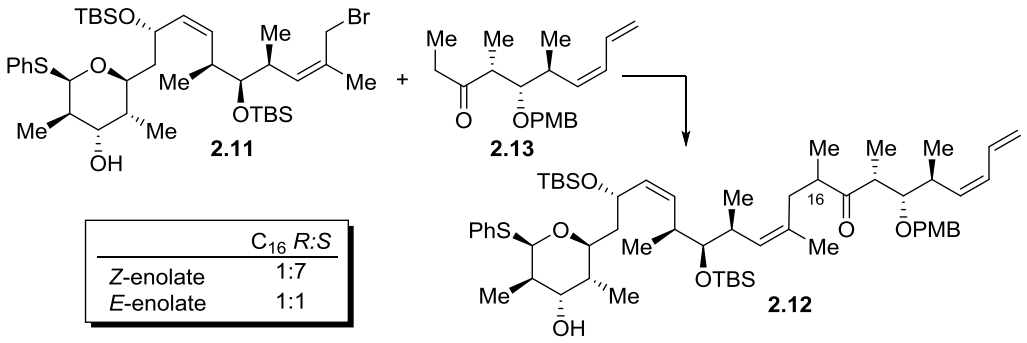
[19] Still, W. C.; Gennari, C. *Tetrahedron Lett*. **1983**, *24*, 4405.
[20] (a) Aicher, T. D.; Kishi, Y. *Tetrahedron Lett*. **1987**, *28*, 3463. (b) Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1985**, *26*, 5585.

Scheme 2.1. Schreiber's Total Synthesis of (+)-Discodermolide



It's worth pointing out that Schreiber's initial plan was to perform a chelation controlled enolate alkylation between allylbromide **2.11** and ethyl ketone **2.13**, which would construct discodermolide backbone **2.12** in one step (Scheme 2.2). Unfortunately the undesired epimer (*S*)-**2.12** predominated when (*E*)- or (*Z*)-enolate derived from ethyl ketone **2.13** was used for the alkylation (subset in Scheme 2.2). It was reasoned that instead of the expected chelation-controlled enolate alkylation, the transition state conformation was set to avoid A(1,3) strain, which led to the undesired diastereomer (*S*)-**2.12**. As a solution, the two-step addition/methylation sequence was used as demonstrated in Scheme 2.1.

Scheme 2.2. Stereoselectivity of Schreiber's Enolate Coupling Reactions



	C_{16} *R:S*
Z-enolate	1:7
E-enolate	1:1

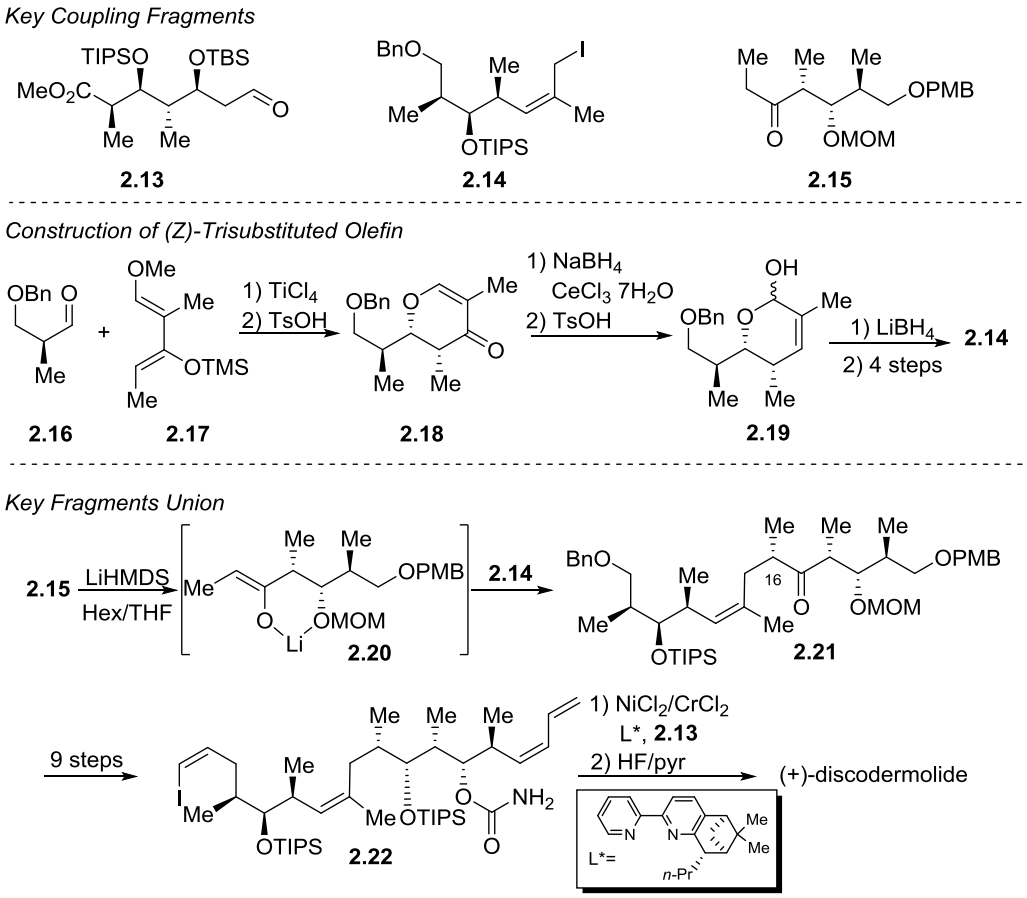
Myles and coworkers reported their total synthesis of (−)-discodermolide in 1997, marking it as the third completed synthesis in the literature. The follow up paper in 2003 presented the details for the natural (+)-isomer (Scheme 2.3).[18e] The molecule was assembled from three advanced fragments (**2.13**, **2.14** and **2.15**). The (*Z*)-trisubstitued olefin in **2.14** was installed *via* titanium mediate hetero-Diels-Alder reaction[21] between aldehyde **2.16** and Danishefsky's diene **2.17**.[22] Subsequent Luche reduction,[23] a Ferrier rearrangement[24] and five more steps furnished allyl iodide **2.14**. Similar to Schreiber's synthesis (Scheme 2.2), Myles also considered an enolate alkylation to build C15-C16 bond. However, contrary to Schreiber's results, the alkylation of (*Z*)-enolate derived from ethyl ketone **2.15** and allyl iodide **2.14**, in a relative non-polar mixed solvent (hexane:THF = 45:55), proceeded smoothly with expected chelation control and gave desired adduct **2.21** with good yield and diastereoselectivity (6:1) at C16.[25] Subsequent

[21] Springer, J. B.; DeBoard, J.; Corcoran, R. C. *Tetrahedron Lett*. **1995**, *36*, 8733.
[22] Danishefsky, S. J.; Pearson,W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc*. **1985**,*107*, 1256.
[23] (a) Luche, J. L.; Gemal, A. L.; *J. Am. Chem. Soc*. **1979**, *101*, 5848. (b) Luche, J. L. *J. Am. Chem. Soc*. **1978**, *100*, 2226.
[24] (a) Ferrier, R. J. *J. Chem. Soc*. **1964**, 5443. (b) Ferrier, R. J.; Overend, W. G.; Ryan, A. E. *J. Chem. Soc., Abstracts* **1962**, 3667.
[25] Yang, G.; Myles, D. C. *Tetrahedron Lett.* **1994**, *35*, 2503.

installation of a *cis*-vinyl iodide using Stork-Wittig olefination[26] and (*Z*)-diene formation using a Peterson type olefination,[27] as well as several additional functional group transformations, furnished the right-half of discodermolide (**2.22**). Unfortunately, a Nozaki-Hiyama-Kishi nickel/chromium-mediated[28] union of vinyl iodide **2.22** and aldehyde **2.13** proceeded in only moderate yield (42%) and selectivity (3:1). After diastereomer separation and global deprotection with HF·pyridine, (+)-discodermolide was completed with a longest linear sequence of 25 steps (44 total steps) in an overall yield of 1.5%.

[26] Stork, G.; Zhao, K. *Tetrahedron Lett*. **1989**, *30*, 2173.
[27] Peterson, D. J. *J. Org. Chem*. **1968**, *33,* 780.
[28] (a) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn*. **1982**, *55*, 561. (b) Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett*. **1985**, *26*, 5585. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc*. **1986**, *108*, 6048. (d) Jin, H.; Uenishi, J.; Christ, W. J.;Kishi, Y. *J. Am. Chem. Soc*. **1986**, *108*, 5644. (e) Aicher, T. D.; Kishi, Y. *Tetrahedron Lett*. **1987**, *28*, 3463.

Scheme 2.3. Myles' Total Synthesis of (+)-Discodermolide



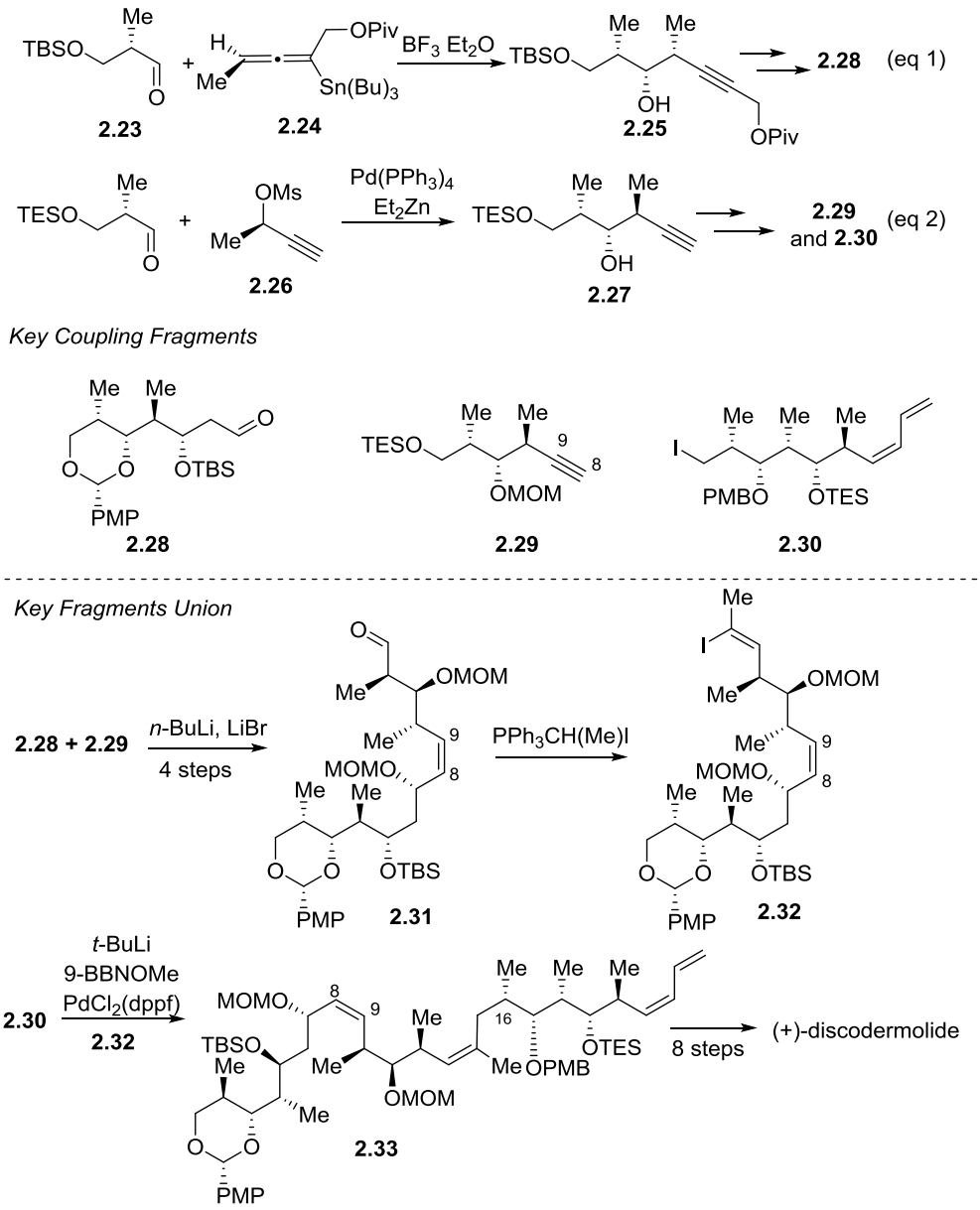
In 1998, Marshall and co-workers have published a total synthesis of (+)-discodermolide that extensively used their asymmetric propargylation for polyketide construction (Scheme 2.4, equation 1 and 2).[18f] (+)-Discodermolide was assembled from three fragments (**2.28**, **2.29** and **2.30**), all of which were prepared by asymmetric propargylation to establish various stereotriad subunits, either in *syn*/*syn* fashion (**2.28** *via* equation 1),[29] or *syn*/*anti* fashion (**2.29** and **2.30** *via* equation 2) (Scheme 2.4).[30] Addition of alkynyl lithium (prepared by deprotonation of **2.29**) to aldehyde **2.28** in the presence of LiBr proceeded in excellent yield and good diastereoselectivity (6:1), and the product

[29] (a) Marshall, J. A.; Lu, Z.-H.; Johns, B. A. *J. Org. Chem*. **1998**, *63*, 817. (b) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem*. **1995**, *60*, 5556.
[30] Marshall, J. A.; Adams, N. D. *J. Org. Chem*. **1998**, *63*, 3812.

alkyne was converted to *cis*-olefin **2.31** bearing requisite aldehyde functionality in four steps. Then Wittig-Zhao olefination[31] of aldehyde **2.31** gave (*Z*)-trisubstituted vinyl iodide **2.32** in only 40% yield. The compound **2.32** was connected to a borane (derived from alkyl iodide **2.30**) *via* Suzuki cross-coupling[32] furnishing tetraene **2.33**. Eight more steps completed the synthesis of (+)-discodermolide with a longest linear sequence of 30 steps (48 total steps) in an overall yield of 1.3%.

[31] Chen, J.; Zhao, K. *Tetrahedron Lett.* **1994**, *35*, 2827.
[32] For review, see: (a) Miyaura, N. *Top. Curr. Chem*. **2002**, *219*, 11. For general reviews of cross-couplings, see: (b) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002.

Scheme 2.4. Marshall's Total Synthesis of (+)-Discodermolide

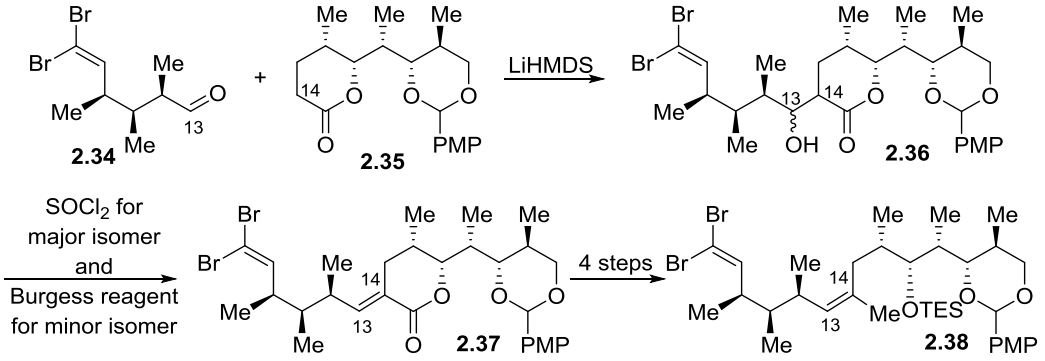


In 1999, a thesis from Evans's group became the fifth documented total synthesis of (+)-discodermolide.[18h] Their route largely relied on Evans asymmetric aldol methodologies[33] to establish stereotriad moieties. The details won't be covered here, but

[33] (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. "*Stereoselective Aldol Condensations*" in Topics in Stereochemistry, New York, 1982; Vol. 13, p. 2. (b) Mukaiyama, T. "*The Directed Aldol Reaction*" in Organic Reactions, New York, 1982; Vol. 28, p 203. (c) Heathcock, C. H.

it is interesting to see a different way to introduce C13-C14 (*Z*)-trisubstitued olefin (Scheme 2.5). Aldehyde **2.34** and lactone **2.35** were adjoined by aldol condensation to furnish **2.36** with 3:1 diastereomerical ratio, which were separated by silica gel chromatography. Each diastereomer of **2.36** was converted to the same product **2.37** under unique dehydration condition, and reduction of lactone **2.37** to methyl substituted alkene successfully installed C13-C14 (*Z*)-trisubstitued olefin (**2.38**).

Scheme 2.5. Evans method to Construct (Z)-Trisubstitued Olefin



The total synthesis of (+)-discodermolide[18n] from the Panek group was an exercise to showcase the use of chiral crotylsilanes in C-C bond construction for polyketide synthesis.[34] The three advanced fragments (**2.42**, **2.43** and **2.44**) were efficiently constructed by addition of crotylsilane **2.40** to an aldehyde **2.39** with Felkin control[35] (Scheme 2.6, equation 3). The (*Z*)-trisubstituted vinylsilane **2.46** was prepared from TMS-alkyne **2.45** (available in five steps from crotylsilane **2.40**) by a sequence of hydrozirconation,[36] iodination, and palladium catalyzed methylation (Negishi coupling), and four more steps to afford central segment **2.43**. The fragments union employed a

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Asymmetric Synthesis; Morrion, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, part B, p 111.

[34] Masse, C. E.; Panek, J. S. *Chem. Rev*. **1995**, *95*, 1293.

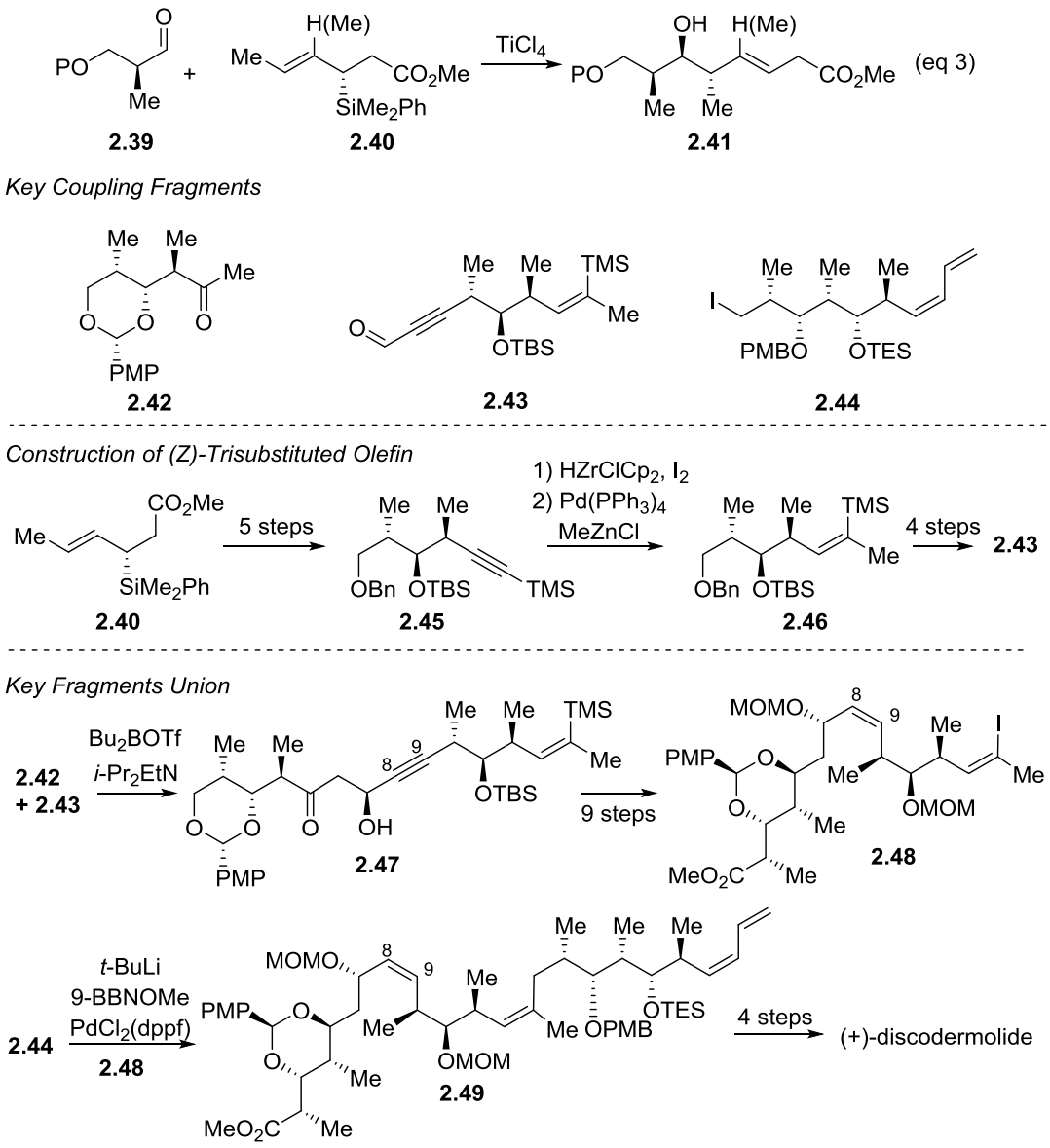
[35] (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, 2199; (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim*. **977**, *1*, 61.

[36] Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc*. **1974**, *96*, 8115.

highly selective 1,4-*syn*-1,5-*anti* aldol between methyl ketone **2.42** and aldehyde **2.43** mediated by dialkylboron triflate.[37] Converting vinylsilane **2.47** to vinyl iodide **2.48** followed by Suzuki coupling with an alkyl iodide **2.44** derived borane gave the skeleton of (+)-discodermolide; four more elaborations completed the synthesis with a longest linear sequence of 27 steps (42 total steps) in an overall yield of 2.1%.

[37] (a) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett*. **1996**, *37*, 8585; (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc*. **2001**, *123*, 9535. (a) Evans, D. A.; Trotter, B.W.; Coleman, P. J.; Cote, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671–8726; (b) Evans, D. A.; Coleman, P. J.; Cote, B. *J. Org. Chem*. **1997**, *62*, 788.

Scheme 2.6. Panek's Total Synthesis of (+)-Discodermolide

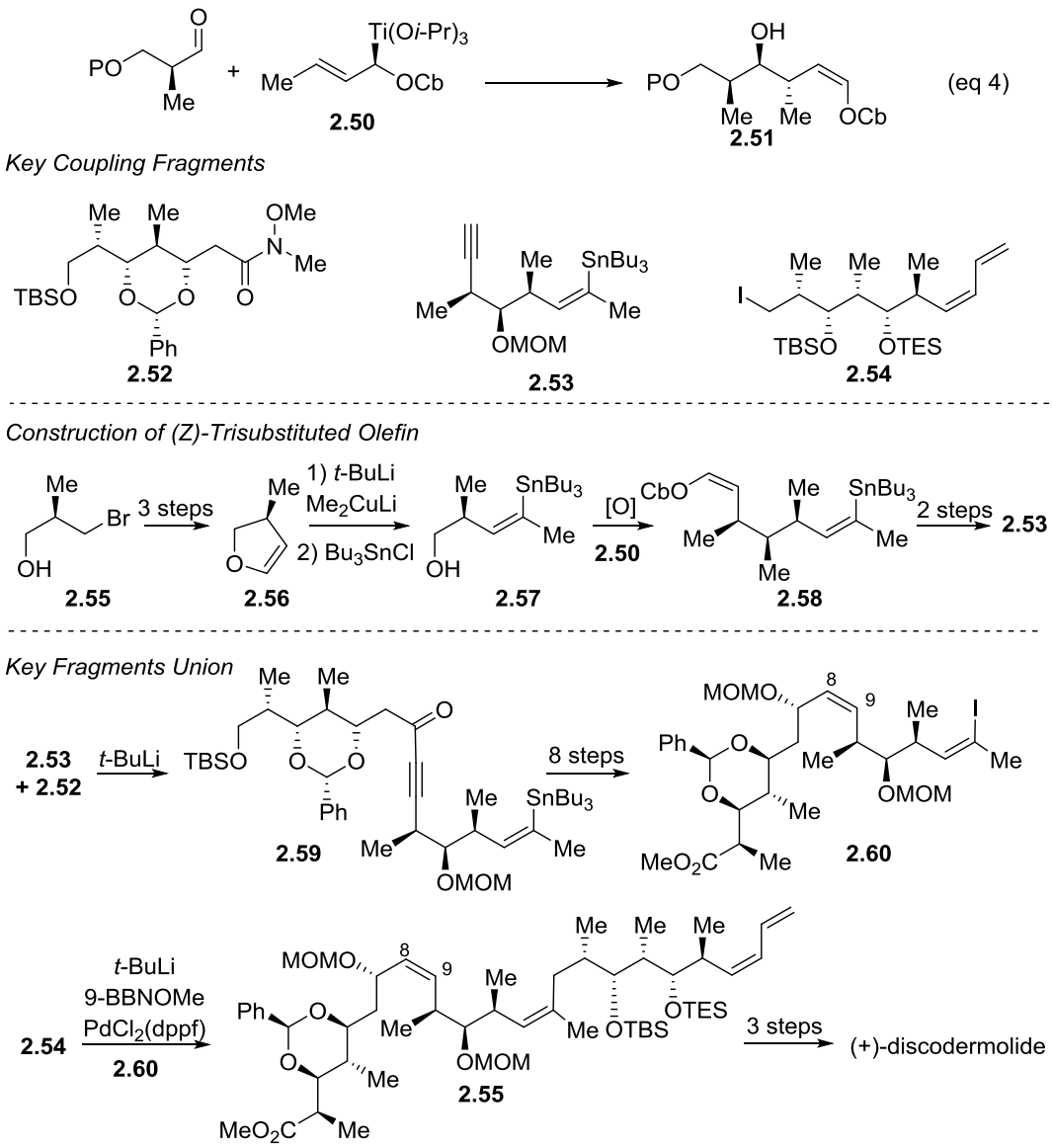


The most recent total synthesis was from Ardisson and co-workers in 2007,[18q] which used crotyltitanate chemistry to construct the *syn*/*anti*-stereotriad from three equally complex fragments (**2.52**, **2.53** and **2.54**) (Scheme 2.7, equation 4). The (*Z*)-trisubstituted vinylstannane **2.53** was prepared from dihydrofuran **2.56** that was available from commercial bromoalcohol **2.55**. Deprotonation of dihydrofuran **2.56** with *t*-BuLi followed by a 1,2-cuprate transfer provided a vinyllithium, which was trapped by tin

chloride furnishing (*Z*)-trisubstituted vinylstannane **2.57**. Subsequent oxidation of **2.57** to an aldehyde followed by crotylation with chiral titanate **2.50** constructed required propionate **2.58** with a *cis*-vinylcarbarmate functionality; **2.58** was deprotonated by *t*-BuLi thereby triggering Fritsch–Buttenberg–Wiechell rearrangement[38] to furnish the central fragment **2.53**. Addition of lithiated alkyne (**2.53**) to Weinreb's amide **2.52** constructed the left-half backbone of discodermolide. Another eight-step transformation provided trisubstituted (*Z*)-vinyl iodide **2.60**, which was used in a Suzuki cross coupling similar to Marshall and Panek's strategies (Scheme 2.5 and 2.6). Three more elaborations completed the synthesis with longest linear sequence of 21 steps in an overall yield of 2.1%.

[38] For a review, see: Knorr, R. *Chem. Rev*. **2004**, *104*, 3795.

Scheme 2.7. Ardisson's Total Synthesis of (+)-Discodermolide



The groups that have been most involved in the chemical synthesis of (+)-discodermolide are the Smith and Paterson laboratories. Both groups have designed and developed several generations of synthetic approaches in order to provide a practical way to prepare this biologically important polyketide. Later, their methods were combined and mixed by a Novartis process research team that successfully delivered 60g of (+)-

discodermolide for early phase clinical trials.[18m] Thus, the three approaches are discussed together below.

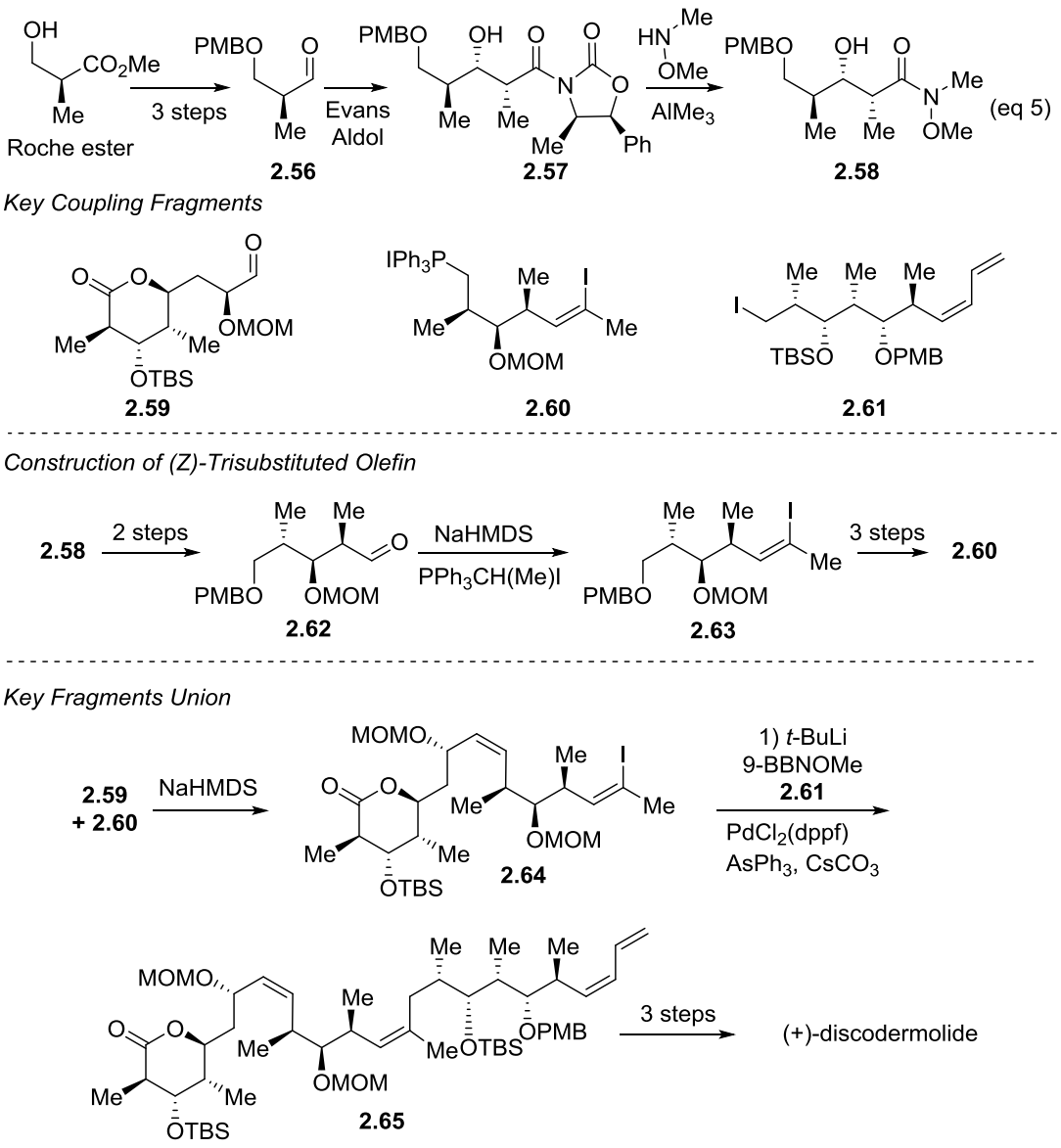
The Smith first-generation synthesis of the unnatural antipode (−)-discodermolide was reported in 1995, marked as the second approach to this molecule.[18c] In order to make the synthesis more convergent and increase the yield for a Wittig phophonium salt preparation, a second generation approach was developed and provided one gram of (+)-discodermolide for pre-clinical study in 2000.[18g] However, further scale-up of the synthesis was limited by ultrahigh pressure and long reaction time (12.8 kbar for 7-10 days) required for Wittig salt preparation. Thus, in 2003, a third generation effort was disclosed enabling the construction of Wittig phosphonium salt at ambient pressure by switching to smaller protecting group (TBS vs. MOM) to reduce the steric hindrance near reaction center. But, this improvement came at the cost of generating more cyclized by-product.[18k]

Smith and co-workers didn't stop improving the synthesis and a fourth-generation approach was reported in 2005 what at the time was the shortest longest-linear sequence of 17 steps (36 total steps) in an impressive 9% overall yield.[18o] Similar to the previous three approaches, one of the central technologies was that each fragment shared the same precursor **2.58**. Thus, it is of great importance to rapidly and reliably produce large quantities of common precursor **2.58** for large scale synthesis. Because of the crystalline solid form of norephedrine-derived Evans *syn*-aldol adduct **2.57** (compared to other amino alcohols derived aldol adducts as liquid),[39] it can be prepared by direct crystallization from crude reaction mixture and only one chromatography was required to synthesize common precursor **2.58** from Roche ester (Scheme 2.8, equation 5). Wittig-

[39] Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77.

Zhao olefination[31] was employed to construct trisubstitued (*Z*)-vinyl iodide **2.63** from aldehyde **2.62** in moderate yield (41%). Due to the deactivated nature of trisubstituted vinyl iodide **2.63** (comparing to trialkyl-substituted olefin), the Wittig phosphonium salt **2.60** was prepared under ambient pressure with no detectable cyclopentane byproducts formation. Wittig union of aldehyde **2.59** and **2.60** followed by Suzuki cross coupling with borane (derived from alkyl iodide **2.61**) provided tetraene **2.65** efficiently. Three more steps completed the synthesis.

Scheme 2.8. Smith's 4th Generation Synthesis of (+)-Discodermolide

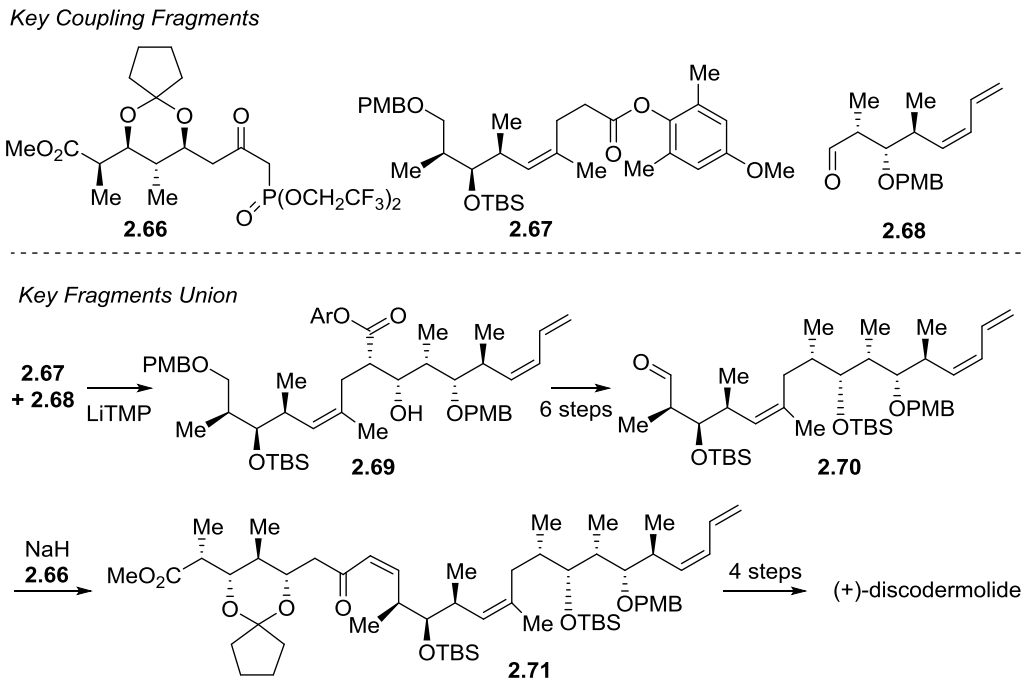


Paterson and co-workers published their first-generation synthesis in 2000. This approach extensively utilized challenging boron mediated aldol reactions to construct and adjoin fragments.[18i] Three years later, a second generation synthesis was reported with a few key changes, but the retrosynthetic strategy was largely analogous to their first generation approach.[18l] In 2004, a third generation was disclosed employing a late-stage Still-Gennari olefination,[19] which greatly improved the overall convergence.[18p] Similar to

the previous two generations of synthesis, the stereotriad in each fragment (**2.66**, **2.67** and **2.68**, Scheme 2.9) was constructed by boron-mediated *anti*-aldol reaction that was well developed in the Paterson laboratory.[40] Fragments union began with an *anti*-ester aldol reaction between aldehyde **2.68** and lithium enolate (derived from ester **2.67**) furnishing right-half backbone of discodermolide (**2.69**) with good diastereoselectivity (6:1). It is worth pointing out that the 2,6-dimethyl-4-methoxylphenyl substitution in ester **2.67** is crucial for the ester aldol reaction, while other ester substitutions resulted lower yield and stereoselection. A three-step reductive removal of the ester moiety followed by another three-step transformation provided an intermediate aldehyde **2.70**, which was subject to Still-Gennari olefination with β-ketophosphonate **2.66** to install the C8-C9 (*Z*)-olefin. The (+)-discodermolide synthesis was completed after another four-step transformation with a longest linear sequence of 24 steps (35 total steps) in an overall yield of 7.8%.

[40] Cowden, C. J.; Paterson, I. *Org. React.* (N.Y.) **1997**, *51*, 1.

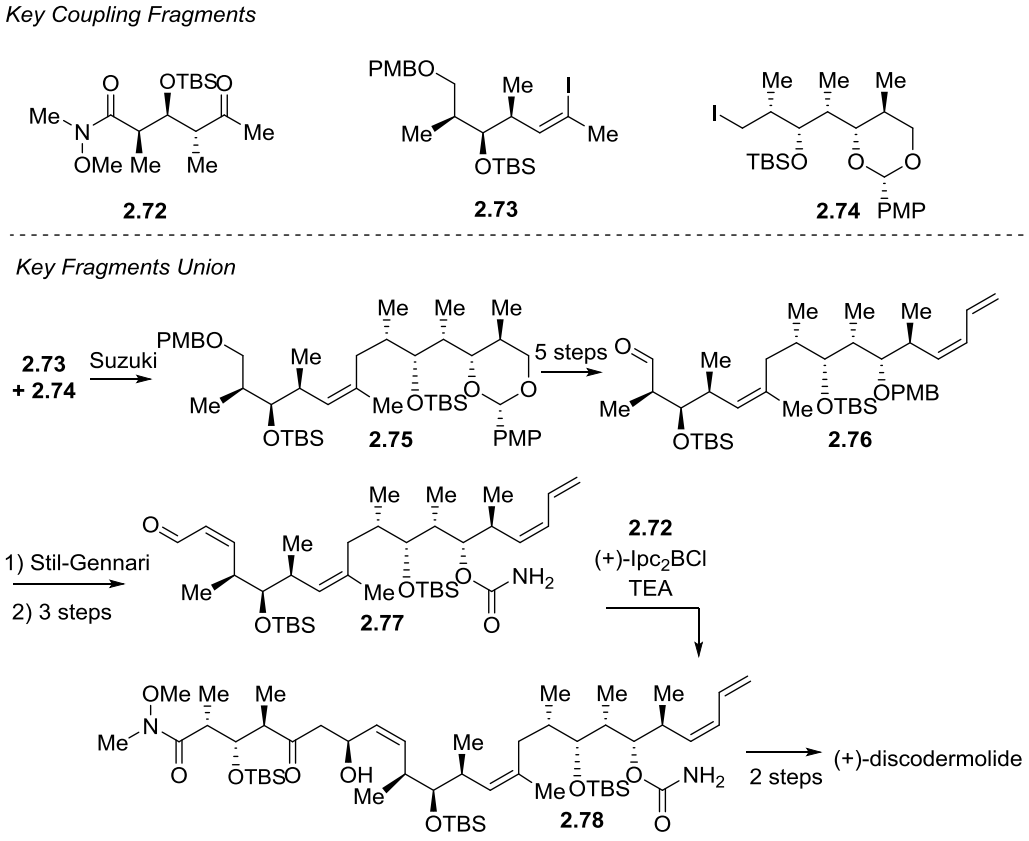
Scheme 2.9. Paterson's 3rd Generation Synthesis of (+)-Discodermolide



Both the Smith and Paterson groups made significant contributions to discodermolide syntheses; as a proof of their success, Novartis produced 60 grams of discodermolide for early phase clinical trials utilizing a hybrid of the Smith second-generation synthesis and the Paterson first-generation endgame.[18m] Multiple kilograms of Weinreb amide (common precursor) **2.58** was prepared *via* a modification of Smith's route without using pyrophoric trimethylaluminum. With a large quantity of common precursor **2.58** in hand, three fragments were rapidly prepared (**2.72 2.73** and **2.74**, Scheme 2.10). Similar to Marshall's approach (Scheme 2.4), vinyl iodide **2.73** underwent Suzuki cross-coupling with a trialkylborane (derived from alkyl iodide **2.74**) furnishing a cleaner reaction compared to the analogous Negishi cross-coupling with *in situ* generated alkylzinc from **2.74**. At this point, aldehyde **2.77** was constructed in order to transit to Paterson first-generation endgame. A reagent controlled asymmetric aldol addition was

employed: (+)-diisopinocamphenylboron enolate[41] of methyl ketone **2.72** added to aldehyde **2.77** furnishing tetraene **2.78** in moderate yield and only 4:1 diastereoselectivity. Two more steps completed the synthesis of (+)-discodermolide with a longest linear sequence of 26 steps (33 total steps) and 17 purifications in an overall yield of 0.65%.

Scheme 2.10. The Novartis 60 g Synthesis of (+)-Discodermolide

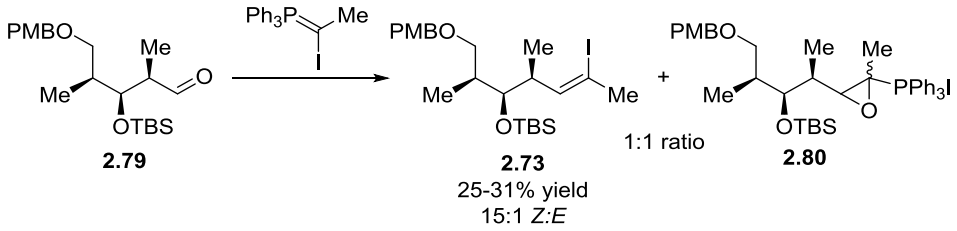


While the Novartis-Smith-Paterson hybrid synthesis is far from optimal, the process was able to deliver 60 grams of (+)-discodermolide that required efforts of 43 chemists over a 20 months period. One of the most difficult and least efficient steps in the

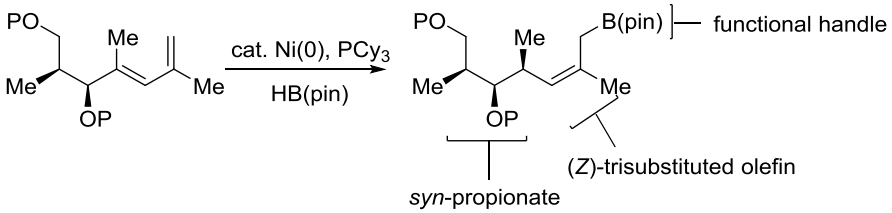
[41] (a) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309. (b) Meyers, A. I.; Yamamoto, Y. *J. Am. Chem. Soc*. **1981**, *103*, 4278. (c) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett*. **1986**, *27*, 4787. (d) Paterson, I.; Lister, M. A. *Tetrahedron Lett*. **1988**, *29*, 585. For related aldol reactions, see: (e) Paterson, I.; Goodman, J. M. *Tetrahedron Lett*. **1989**, *30*, 997. (f) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett*. **1989**, *30*, 7121. (g) Paterson, I.; McClure, C. K. *Tetrahedron Lett*. **1987**, *28*, 1229.

hybrid synthesis was the Wittig-Zhao olefination constructing (*Z*)-trisubstituted vinyl iodide **2.73**, which only gave 25-31% yield (Scheme 2.11). The low yield was caused by the formation of large percentage of undesired epoxide **2.80** and the inherent instability of vinyl iodide **2.73**.[42] Thus, it is of great importance to develop a method that could effectively construct the challenging C13-C14 (*Z*)-trisubstituted olefin, preferably a catalytic process that concomitantly establishes the *syn*-propionate moiety adjacent to the olefin as well as a functional handle for further fragment union. It was considered that Ni-catalyzed diastereoselective hydroboration of dienol (Chapter 1) could serve as a central methodology to rapidly construct (+)-discodermolide (Scheme 2.12).

Scheme 2.11. The Novartis Hybrid Synthesis of (Z)-Trisubstituted Vinyl Iodide



Scheme 2.12. Ni-Catalyzed Hydroboration of Dienol for Discodermolide Synthesis



Another consideration is that every previous approach to discodermolide started from fairly expensive Roche ester (~$20/g from Aldrich). A catalytic method that constructs similar building blocks from inexpensive feedstocks, such as asymmetric hydroformylation of terminal olefins (Chapter 3), would be valuable to organic synthesis. Herein, (+)-discodermolide was synthesized by three catalytic stereoselective borylation

[42] Arimoto, H.; Kaufman, M. D.; Kobayashi, K.; Qiu, Y.; Smith, A. B. III. *Synlett.* **1998**, 765.

reactions developed in the Morken laboratory, which also marked as the first Roche ester-free approach to this biological active molecule.

2.3 Total Synthesis of (+)-Discodermolide

2.3.1 Original Retrosynthetic Analysis

In our retrosynthetic analysis, (+)-discodermolide was disconnected to three equally complex fragments by cleaving the C8-C9 *cis*-double bond and the C15-C16 bond for a convergent synthesis. This renders β-ketophosphonate **2.81**, (*Z*)-trisubstituted olefin **2.82** and diene tail **2.83** as key fragments. The C15-C16 bond could be formed by a homologation of secondary boronic ester **2.82** and enantiomerically enriched organolithium **2.83** to accomplish fragment union. Similar to Paterson's third-generation synthesis (Scheme 2.9),[18p] a challenging late stage Still-Gennari olefination between β-ketophosphonate **2.81** and an aldehyde derived from **2.82** could furnish the C8-C9 *cis*-double bond.

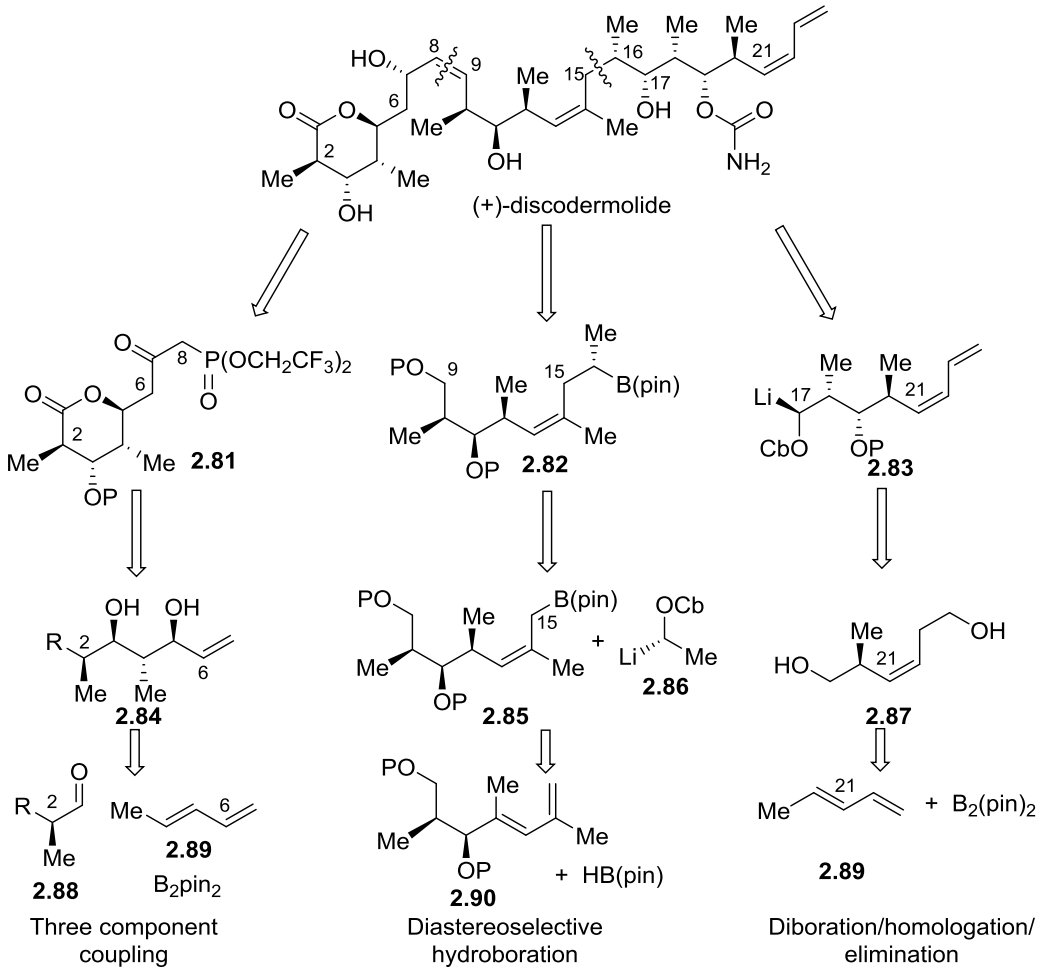
The synthesis features rapid construction of three advanced fragments *via* three catalytic stereoselective borylation reactions developed in our laboratory: Ni-catalyzed borylative diene-aldehyde three-component coupling reaction (BDAC) (Chapter 4),[43] Ni-catalyzed diastereoselective hydroboration of chiral dienols (Chapter 1), and Pt-catalyzed asymmetric diene diboration.[44] A highly diastereoselective Ni-catalyzed borylative diene (**2.89**) aldehyde (**2.88**) coupling reaction would give 1,3-diol **2.84**, which has a carboxylic acid equivalent (R-substituent) and a terminal olefin; further transformation would convert **2.84** to β-ketophosphonate **2.81**. The diene fragment **2.83** could arise from

[43] Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 7576.
[44] (a) Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134. (b) Schuster, C. H.; Li, B.; Morken, J. P. *Angew. Chem. Int. Ed*. **2011**, *50*, 7906.

selective elimination of 1,6-diol **2.87** that could be synthesized by an asymmetric Pt-catalyzed 1,4-diboration of *trans*-pentadiene **2.89**, followed by bis-Matteson homologation[45]-oxidation sequence. The chiral secondary boronic pinacol ester moiety in **2.82** could be prepared from a homologation of allylboronic pinacol ester **2.85** with an enantiomerically enriched organolithium **2.86** and the allylboronic pinacol ester **2.85**. The later (**2.85**) is available from a successful Ni-catalyzed diastereoselective hydroboration of chiral dienol **2.90** which constructs the trisubstituted (*Z*)-olefin and adjacent propionate moiety at the same time (Chapter 1). The synthesis also has the advantage that all advanced building blocks would come from readily available, inexpensive and achiral hydrocarbons.

[45] Sadhu, K.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.

Scheme 2.13. Retrosynthetic Analysis of (+)-Discodermolide

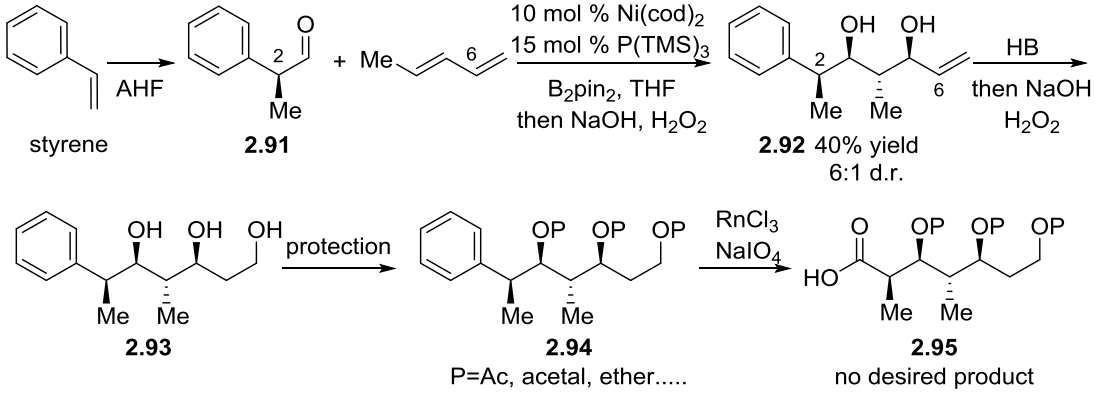


2.3.2 Preparation of C1-C8 Fragment

As proposed in our retrosynthetic analysis (Scheme 2.13), the borylative three-component coupling was tested. Our laboratory disclosed one example of the Ni-catalyzed borylative diene aldehyde coupling using α-chiral aldehyde **2.91**,[43] which provided Felkin adduct **2.92** with 40% yield and 6:1 dr (Scheme 2.14). The required *syn/anti/anti*-stereotetraiad was constructed in one catalytic step where the chirality originated from the aldehyde **2.91**, a product of asymmetric hydroformylation of

styrene.[46] This is very exciting because the C1-C8 fragment would be constructed without using a Roche ester or chiral auxiliary. Most importantly, the valuable terminal olefin could be converted to a primary alcohol **2.93**, a precursor for assembly of β-ketophosphonate moiety **2.81** (Scheme 2.13). Originally, oxidative cleavage of phenyl ring[47] in **2.94** was considered to generate requisite carboxylic acid **2.95** (Scheme 2.14). Unfortunately, after extensive reaction screening of conditions and protecting groups, no product other than decomposition of starting material could be obtained. This situation might be caused by the harsh oxidative reaction condition that is incompatible with highly oxygenated starting material **2.94**.

Scheme 2.14. Original Borylative Diene Aldehyde Coupling



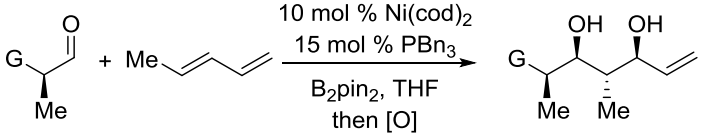
Thus, it was of great importance to find another chiral aldehyde whose substitution can be converted to a carboxylic acid under mild conditions. Several α-chiral aldehydes were then screened (Table 2.1). To effect borylative coupling, tribenzylphosphine [$P(Bn)_3$] was used as a ligand. This is a convenient, non-pyrophoric alternative to tris(trimethylsilyl)phosphine [$P(TMS)_3$] which was originally developed for this reaction (see Chapter 4). The β-siloxyaldehyde **2.96** gave desired product **2.97** with

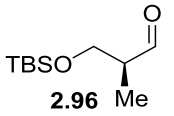
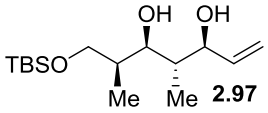
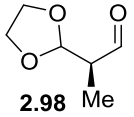
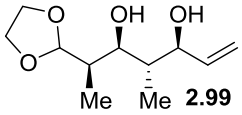
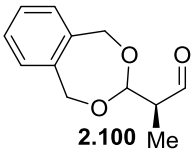
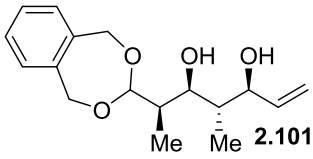
[46] For a review, see: Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007,** *40,* 1251.
[47] For a review, see; Mander, L. N.; Williams, C. M. *Tetrahedron* **2003**, *59*, 1105.

only 2:1 dr, though the product could be converted to the carboxylic acid required for lactonization (Table 2.1, entry 1). It was considered that the low diastereoselectivity was due to the similarity in size between hydroxylmethyl and methyl groups in **2.96**; thus, a more steric demanding cyclic acetal-containing aldehyde was considered. As expected, 1,3-dioxolane derived aldehyde **2.98** gave better diastereoselectivity; however, selective removal of dioxolane protecting group proved to be challenging in the presence of other acetal protecting group (Table 2.1, entry 2). Developed by Kibayashi and co-workers,[48] the *o*-xylyl acetal protecting group was employed because it can be selectively removed under neutral hydrogenation conditions. Accordingly, aldehyde **2.100** was prepared and subjected to the standard three-component coupling reaction conditions. After oxidation, the desired 1,3-diol **2.101** was obtained with good diastereoselectivity (6:1) as indicated by crude ^{1}H-NMR. However, a new inseparable compound was also formed (~1:1 ratio) along with desired product **2.101**. Later, the inseparable compound was identified as constitutional isomer **2.102**, which resulted from transketalization of **2.101** during chromatography (Scheme 2.15, equation 6). In order to avoid such rearrangement, the concentrated crude reaction mixture was directly treated with 2,2-dimethoxylpropane and a catalytic amount of weak acid, pyridinium *p*-toluenesulfonate, to install the acetonide protecting group that rendered **2.103** as a stable and isolable product. If stronger acid was used for acetonide formation, transketalization was also observed. After extensive reaction optimization, **2.103** was obtained directly from aldehyde **2.100** without isolating any intermediate. Importantly, it was also determined that the catalyst loading for the three-component coupling reaction can be lowered to 5 mol % while maintaining good yield and stereoselection (Scheme 2.15, equation 7).

[48] Machinaga, N.; Kibayashi, C. *Tetrahedron Lett*. **1989**, *30*, 4165.

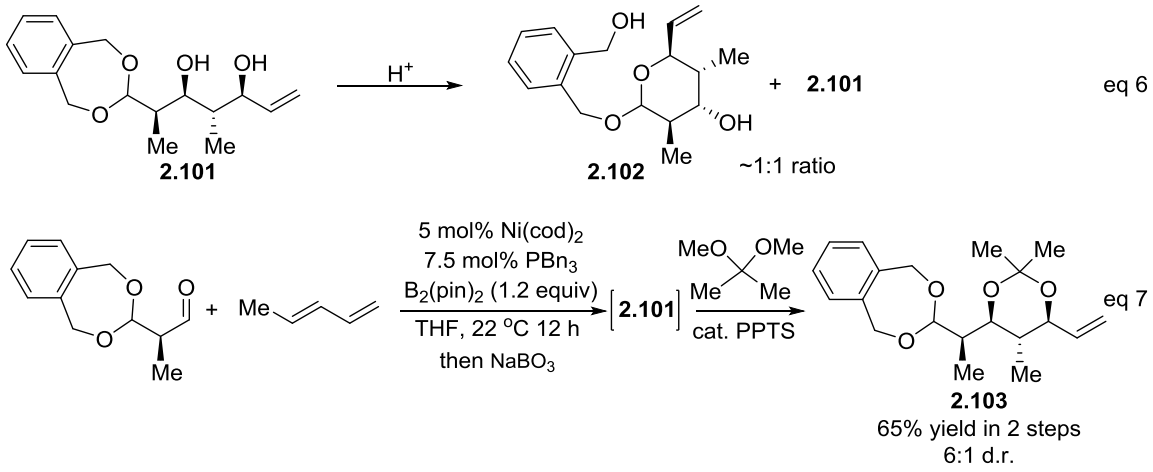
Table 2.1. Selected Aldehydes for Borylative Diene Aldehyde Coupling



entry	aldehyde	product	d.r. [a]	yield (%)
1[b]	 **2.96**	 **2.97**	2:1	52
2[c]	 **2.98**	 **2.99**	5:1	~14[d]
3[b]	 **2.100**	 **2.101**	6:1	~47[d]

[a] d.r. was determined by ^{1}H-NMR and referred to Felkin/*anti*-Felkin products. [b] Oxidation with $NaBO_3$. [c] Oxidation with $NaOH/H_2O_2$. [d] Contaminated by transketalization product.

Scheme 2.15. Problematic Transketalization and Its Solution

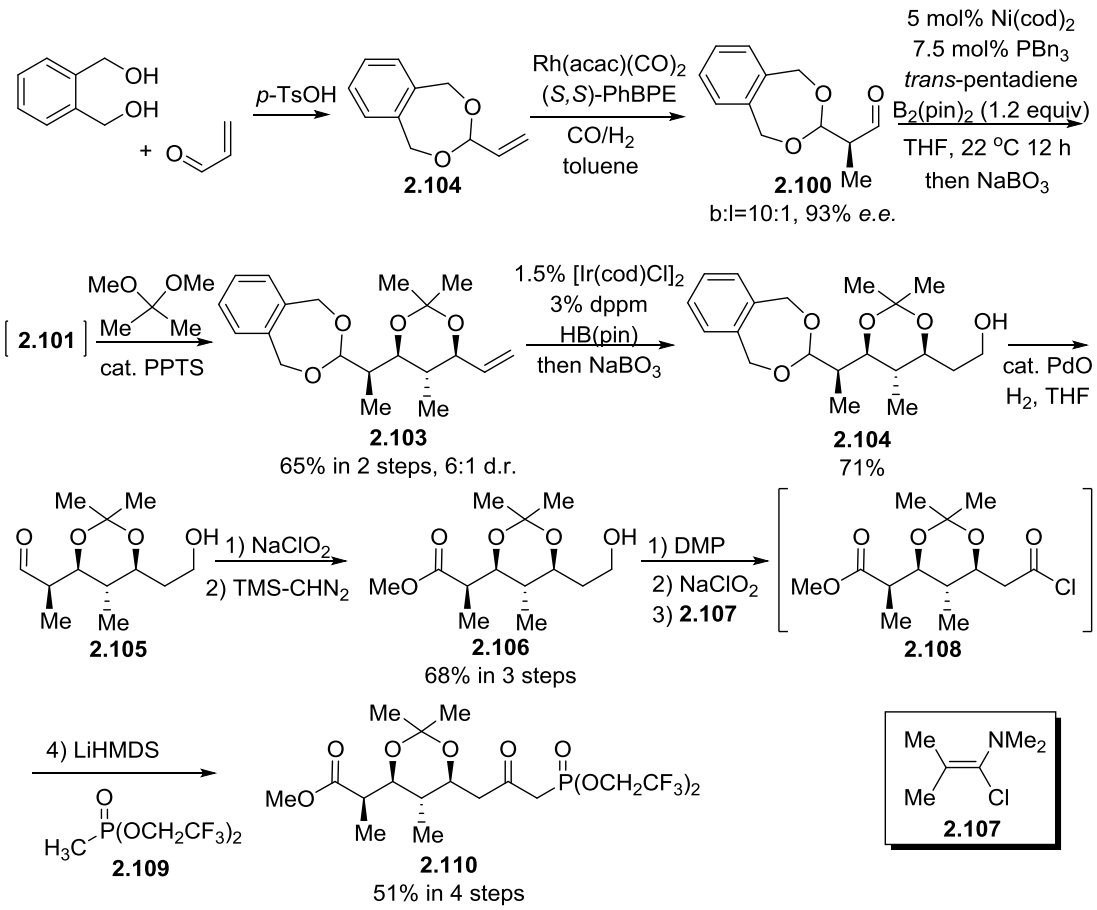


At the early stage of aldehyde screening (Table 2.1), the racemic aldehyde **2.100** was prepared in five steps from 2-methyl-1,3-propandiol, and rapid preparation of enantiomerically enriched **2.100** still remained a challenging task. Thus, a new methodology, asymmetric hydroformylation of terminal olefins, was developed to

address this issue and delivered large quantities of the important building block **2.100**. More than seven grams of optically active aldehyde **2.100** was prepared in one step from *o*-xylyl acetal protected acrolein **2.104** (Chapter 3), while it would cost six steps from Roche ester. A reliable supply of aldehyde **2.100** and optimized borolative diene-aldehyde coupling reaction allowed a quick access to the intermediate **2.103**. Accordingly, the next step of converting the terminal olefin to a primary alcohol was examined (Scheme 2.16). Similar to the observation made by Shioiri and co-workers in their synthesis of Calyculin A, [49] hydroboration (e.g. BH_3, 9-BBN, and catechol borane)/oxidation sequence applied to terminal olefin **2.103** in the presence of the adjacent ketal functionality gave desired primary alcohol **2.104** with irreproducible and poor yields. The strong Lewis acidity of the involved trialkylborane may cause decomposition of the Lewis basic ketal moiety. Thus, hydroboration with less Lewis acidic pinacolborane was considered.[50]

[49] Kabeya, M.; Hamada, Y.; Shioiri, T. *Tetrahedron,* **1997**, *53*, 9777.
[50] Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868.

Scheme 2.16. C1-C8 Fragment Synthesis



An iridium catalyzed hydroboration[51] of terminal olefin **2.103** with pinacolborane furnished the corresponding less Lewis acidic alkylboronic acid pinacol ester, and subsequent mild sodium perborate oxidation delivered primary alcohol **2.104** with good and reproducible yield (71%). As designed, selective removal of the *o*-xylyl acetal in the presence of acetonide protecting group was achieved under neutral hydrogenation conditions with a catalytic amount of palladium oxide and atmospheric pressure of hydrogen gas; the intermediate product aldehyde **2.105** was used for next step without

[51] Yamamoto, Y.; Fijukawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron,* **2004**, *60*, 10695.

further purification. Subsequent Pinick oxidation[52] of the crude aldehyde **2.105** gave corresponding carboxylic acid, which was esterified by treatment with a hexane solution of $TMSCHN_2$, furnishing methylester **2.106** in good yield over four steps. Stepwise oxidation of **2.106** using Dess-Martin periodinane[53] followed by Pinick oxidation,[52] provided a carboxylic acid that was treated with Ghosez reagent **2.107**[54] to generate acid chloride **2.108** under mild condition. It was necessary to use the Ghosez reagent **2.107** to synthesize acyl chloride **2.108** because only neutral reaction condition allowed survival of the acid-sensitive ketal protecting group (Scheme 2.17). The acyl chloride **2.108** was reacted immediately with the phosphoryl anion generated by deprotonation of **2.109**.[55] Pleasingly, the acylation proceeded smoothly to afford C1-C8 fragment **2.110** with good yield over four steps. Starting from readily available 1,2-benzenedimethanol,[56] β-ketophosphonate **2.110** was conveniently prepared on several hundred milligrams scale in 12 steps without using Roche ester or any chiral auxiliary.

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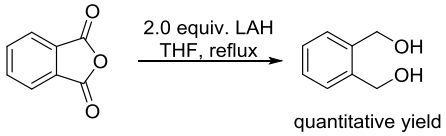
[52] (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand*. **1973**, *27*, 888. (b) Bal, B. S.; Childers, W. E. J.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091. (c) Mann, J.; Thomas, A. *Tetrahedron Lett*. **1986**, *27*, 3533.

[53] (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem.* Soc. **1991**, *113*, 7277.

[54] Devos, A.; Remion, J.; Frisque-Hesbain, A. M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180.

[55] Yu, W.; Su, M.; Jin, Z. *Tetrahedron Lett.* **1999**, *40*, 6725.

[56] 1,2-benzenedimethanol is commercially available from Aldrich ($40.2/g), or it is easily prepared from cheap phthalic anhydride ($51/500g) in one step in almost quantitative yield.



Scheme 2.17. Preparation of Acyl Chloride under Neutral Conditions

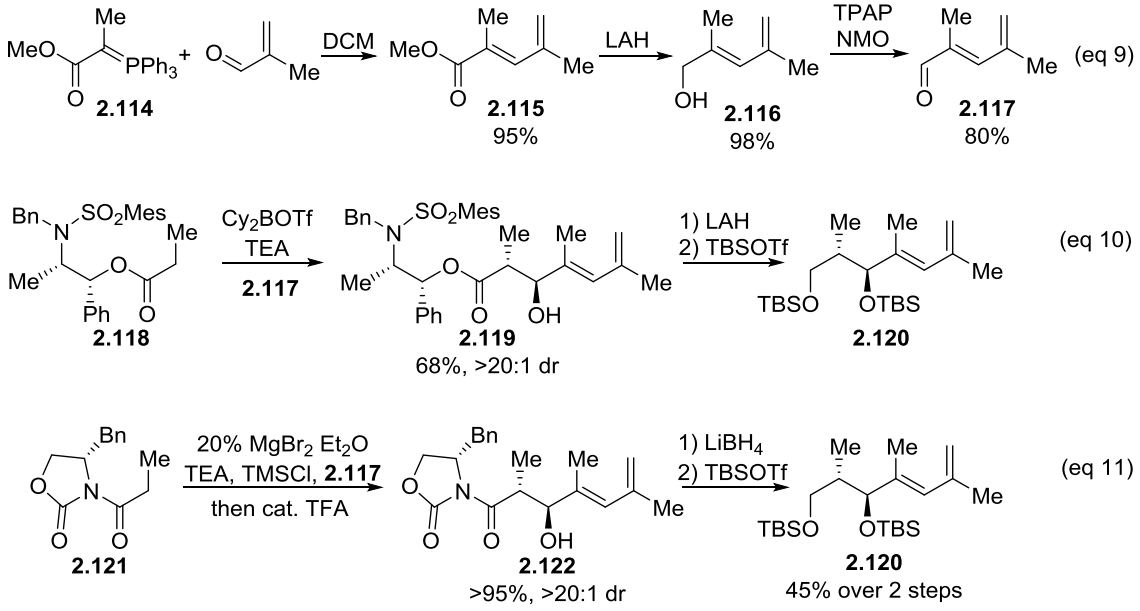
2.3.3 Preparation of C9-C16 Fragment

Efficient construction of C9-C16 fragment largely relied on rapid preparation of chiral dienol **2.90** (Scheme 2.13). According to previous observations,[57] bis-TBS protected dienol ether **2.120** could participate in the Ni-catalyzed diastereoselective hydroboration (Chapter 1, Table 1.2, entry 10), while a very similar diene but with a PMB-protected primary alcohol was surprisingly inactive. This difference in reactivity might attributed to intramolecular binding of the basic benzyl ether to the nickel center inhibiting the hydroboration process, similar to terminal alkene and Weireb amide containing substrates (Chapter 1, Table 2.1). Thus, it is necessary to construct enantiomerically-enriched dienol ether **2.120** with a bulky and non-chelating TBS-protecting group. Considering the *anti*-relationship of the propionate in **2.120**, an *anti*-aldol reaction was attempted. The synthesis of the required dienal **2.117** for aldol reaction was accomplished with a high yielding three-step sequence involving an olefination between methacrolein and a stabilized Wittig reagent **2.114**, an $LiAlH_4$ reduction and a TPAP catalyzed oxidation to afford aldehyde **2.117** with good yield and >20:1 (*E*)-selectivity (Scheme 2.18, equation 9). A number of *anti*-aldol reactions were then evaluated on aldehyde **2.117**. Chiral auxiliary containing ethyl ketone **2.118**[58] condensed with aldehyde **2.117** furnishing desired *anti*-aldol adduct **2.119** with good yield and

[57] Ely, R. J. Ph.D. Thesis, Boston College, 2012.
[58] Abiko, A. *Org. Syn*. **2002**, *79*, 109.

excellent selectivity under Abiko-Massamune aldol[59] reaction conditions (Scheme 2.18, equation 10). However, Evans *anti*-aldol[60] was superior in this case due to its easier reaction set-up and more readily available reagents compared to the Abiko-Massamune aldol reaction. Subjecting aldehyde **2.117** to standard Evans *anti*-aldol reaction conditions, **2.122** was isolated with excellent yield and diastereoselectivity (Scheme 2.18, equation 11). In both cases, the auxiliaries were removed under reductive conditions furnishing a 1,3-diol, which was protected as bis-TBS ether **2.120**.

Scheme 2.18. Synthesis of Chiral Dienol Ether by *anti*-Aldol Reactions



Though both auxiliary based *anti*-aldol reactions in Scheme 2.18 provided dienol ether **2.120** efficiently in a reasonably short sequence, it would be of great value if **2.120** can be constructed *via* a catalytic method from readily available materials. The first thought was asymmetric catalytic aldol reactions; unfortunately, very few catalytic *anti*-

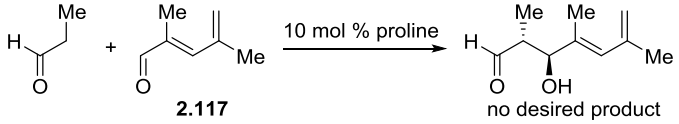
[59] (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc*. **1997**, *119*, 2586. (b) Inoue, T.; Liu, J.-F.;Buske, D. C.; Abiko, A. *J. Org. Chem*. **2002**, *67*, 5250. (c) ref. 58
[60] Evans, D. A.; Tedrow, J. S., Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392.

aldol[61] or crotylation[62] reactions are highly enantio- and diastereoselective with aliphatic or α,β-unsaturated aldehydes.[63] A former group member, Dr. Robert J. Ely,[57] employed an Ir-catalyzed transfer hydrogenation reaction, developed by Krische and co-workers.[64] The reaction between alcohol **2.116** and crotyl acetate established the *anti*-propionate moiety in **2.123** with good diastereo- and enantioselectivity (Scheme 2.19). Desired diene **2.120** was obtained after a series of subsequent transformations including a Pt-catalyzed diboration/oxidation,[65] oxidative cleavage of 1,2-diol, reduction and TBS-protection. While Ir-catalyzed transfer hydrogenation reaction constructed desired *anti*-aldol moiety efficiently, we didn't pursue this method further because the transfer hydrogenation reaction only gave partial conversion after 48 h at 60 ^{o}C and too many transformations were required converting **2.123** to bis-TBS ether substrate **2.120**. Thus, a shorter and more efficient method needed to be developed to construct the important precursor **2.120** for the C9-C16 fragment.

[61] (a) Denmark, S. E.; Heemstra Jr., J. R.; Beutner, G. L. *Angew. Chem., Int. Ed*. **2005**, *44*, 4682. (b) Brodmann, T.; Lorenz, M.; Schäckel, R.; Simsek, S.; Kalesse, M. *Synlett* **2009**, 174.

[62] For a review on catalytic asymmetric carbonyl allylation, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.

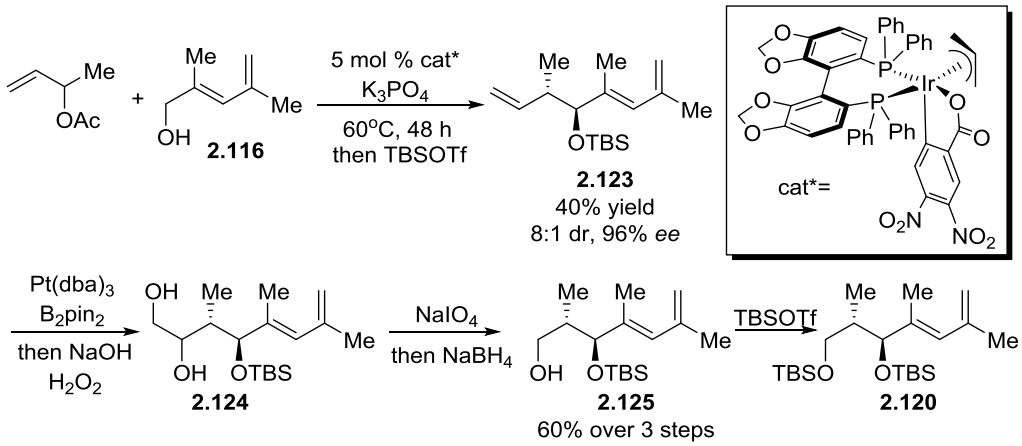
[63] The proline catalyzed cross-aldol reaction was unsuccessful with aldehyde **2.117**, see; Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2002**, *124*, 6798.



[64] For references, see Chapter 1, Section 1.1.

[65] (a) Coombs, J. R.; Haeffner, F.; Kliman L. T.; Morken, J. P. *J. Am.Chem.Soc.* **2013**, *135,* 11222. (b) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem.Soc*. **2009**, *131*, 13210.

Scheme 2.19. Synthesis of Chiral Dienol Ether *via* Transfer Hydrogenation



Besides *anti*-aldol and crotylation reactions, another class of methods to establish *anti*-propionate moieties is chelation controlled neucleophilic addition to a β-hydroxyl aldehyde, using an existing stereogenic center to influence the introduction of new stereocenter(s) (Scheme 2.20).[66] Moreover, the outcome of the new stereocenter(s) could be controlled by a number of methods, such as Felkin-Ann selectivity,[67] Cram-chelation model.[68] Thus, in order to construct 1,2-*anti*-propionate moiety in **2.127**, chelation controlled neucleophilic addition should be applied, which usually requires using a small protecting group, such as MOM, Bn, and Me ether protected alcohol (Scheme 2.20,

[66] (a) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989. (b) Koskinen, A. *Asymmetric Synthesis of Natural Products*; Wiley: Chichester, NY, 1993. (c) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. 1993, 93, 1307. (d) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: Weinheim, Germany, 1996. (e) Nicolaou, K. C.; Snyder, S.A. *Classics in Total Synthesis II*: More Targets, Strategies, Methods; Wiley-VCH: Weinheim, Germany, 2003. (f) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, Germany, 2009.

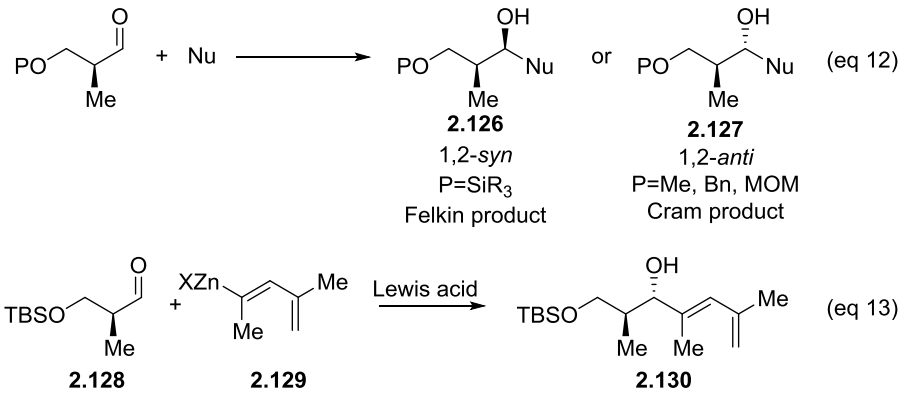
[67] (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, *9*, 2199. (b) Cherest, M.; Felkin, H. *Tetrahedron Lett*. **1968**, 9, 2205. (c) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett*. **1976**, *17*, 155. (d) Anh, N.; Eisenstein, O. *Nouv. J. Chim*. **1977**, *1*, 61. (e) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

[68] (a) Cram, D. J.; Elhafez, F. A. A. *J. Am. Chem. Soc*. **1952**, *74*, 5828. (b) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc*. **1959**, *81*, 2748. (c) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc*. **1968**, *90*, 4019.

equation 12).[69] However, as aforementioned, a bulky and non-chelating silyl protecting group of primary alcohol is crucial for the Ni-catalyzed hydroboration to proceed, and the corresponding starting material, β-siloxyl aldehyde **2.128**, disfavors chelation and usually gave Felkin 1,2-*syn*-product **2.126**. To avoid a protecting group swap, it would be extremely valuable if the β-siloxyl aldehyde **2.128** underwent chelation controlled neucleophilic addition itself and constructed Cram 1,2-*anti*-product **2.127** selectively. Unfortunately, there are only limited methods to promote chelation controlled additons to β-siloxyl aldehydes or ketones. For example, Evans and co-workers reported the ability of Me_2AlCl and $MeAlCl_2$ to chelate β-siloxyl aldehydes in Mukaiyama aldol reactions.[70] Recently, Walsh and co-workers also demonstrated that chelation controlled addition of organozinc reagents to β-siloxyl aldehydes could be accomplished in the presence of a remarkable zinc-derived Lewis acid, EtZnONf, EtZnOTf,[71] or $ZnBr_2$.[72] Thus, it was proposed that desired 1,2-*anti*-product **2.130** could be accessed by a Lewis acid-mediated addition of vinylzinc **2.219** to β-siloxyl aldehyde **2.218** under chelation-controlled process (Scheme 2.20, equation 13).

[69] (a) Keck, G. E.; Castellino, S. *J. Am. Chem. Soc*. **1986**, *108*, 3847. (b) Reetz, M. T. *Acc. Chem. Res*. **1993**, *26*, 462.
[70] Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc*. **2001**, *123*, 10840.
[71] G. R. Stanton, M. C. Kauffman, P. J. Walsh, *Org. Lett.* **2012**, *14***,** 3368.
[72] Jeon, S.-J.; Fisher, E. L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc*. **2006**, *128*, 9618.

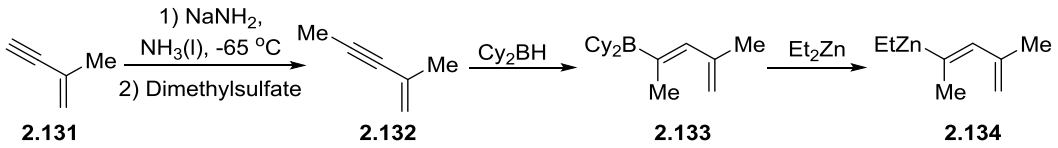
Scheme 2.20. 1,2-Asymmetric Induction for β-Hydroxyl Aldehyde



Vinylzinc **2.134** could be generated *in situ* using Srebnik/Oppolzer procedure:[73] hydroboration of enyne **2.132** followed by transmetalation of vinyl group in **2.133** from B to Zn with Et_2Zn (Scheme 2.21). However, the starting material, simple enyne **2.132**, was a challenging compound to prepare due to its low molecular weight and low boiling point. Common terminal alkyne alkylation[74] of commercial enyne **2.131**, when carried out in THF or ether solution, did produce product enyne **2.132** as determined by crude ^{1}H NMR. However, all attempts of its isolation and purification from solution phase failed due to unavoidable solvent contamination. After studying a number of reaction conditions and solvent screening, it was identified that a reaction sequence of deprotonation of enyne **2.131** with sodium amide in liquid ammonia, methylation with dimethylsulfate, evaporating ammonia solvent and subsequent *in situ* distillation provided enyne **2.132** as a colorless liquid (bp~45 ^{o}C) in 55% reproducible yield on multiple grams scale. The successful preparation of enyne **2.132** paved the way to access key intermediate nucleophile **2.134** for the dienol ether's (**2.120**) synthesis.

[73] (a) Srebnik, M. *Tetrahedron Lett*. **1991**, *32*, 2449. (b) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170. (c) Oppolzer, W.; Radinov, R. N.; Brabander, J. D. *Tetrahedron Lett*. **1995**, *36*, 2607. (d) Oppolzer, W.; Radinov, R. N.; El-Sayed, *E. J. Org.Chem*. **2001**, *66*, 4766.
[74] Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988.

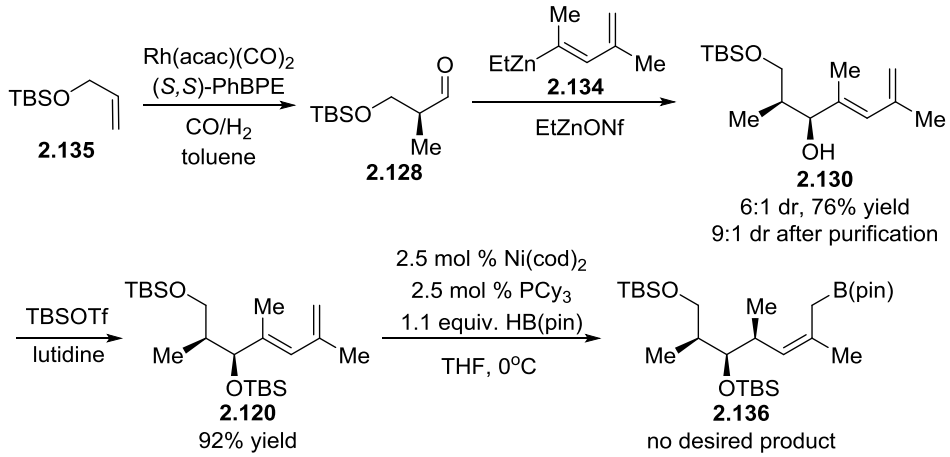
Scheme 2.21. Preparation of Vinylzinc Nucleophile



Following the procedure reported by Walsh and co-workers,[71] a chelation controlled addition of *in situ* generated vinylzinc **2.134** (Scheme 2.22) to the TBS-protected β-hydroxyl aldehyde **2.128** was accomplished in the presence of EtZnONf to afford diene **2.130** with good yield and diastereoselectivity (Scheme 2.22). EtZnONf was the most efficient Lewis acid compared to EtZnOTf, $ZnBr_2$, and Me_2AlCl.[75] It is noteworthy that diene **2.130** is constructed in only two steps including an asymmetric hydroformylation of allyl ether **2.135** without using any chiral auxiliary or Roche ester (Chapter 3). Subsequent TBS-protection of the secondary alcohol in **2.130** gave desired diene **2.120** and set the stage for Ni-catalyzed hydroboration. However, no conversion was observed after subjecting diene **2.120** to standard reaction conditions (Scheme 2.22). It was suspected that an inseparable impurity in starting material **2.120** (<5% as determined by ^{1}H NMR) inhibited the Ni-catalyzed hydroboration reaction. Unfortunately, no purification method was able to remove the unknown impurity in diene **2.120**.

[75] EtZnOTf, $ZnBr_2$, and Me_2AlCl did provide desired product **2.130**, but with lower yield and diastereoselectivity.

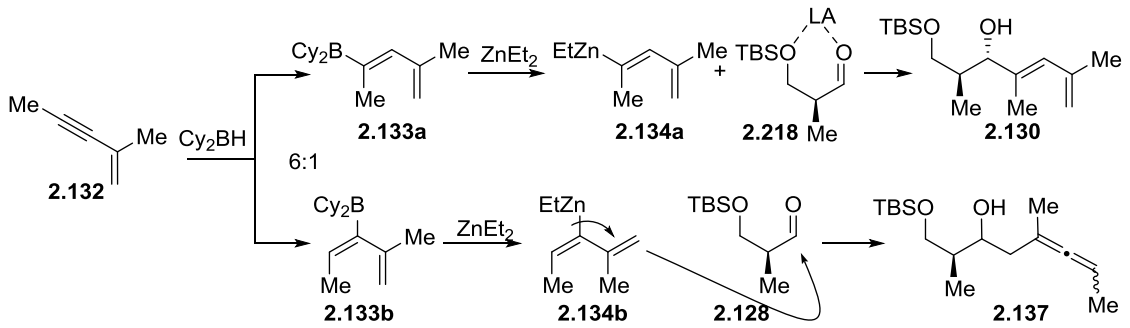
Scheme 2.22. Synthesis of Dienol Ether



At that point, the structure and properties of the impurity remained unknown, yet it was important and interesting to identify the impurity which might help prevent its formation or facilitate purification. After extensive characterization, the ^{13}C NMR of contaminated diene **2.120** showed a characteristic peak of an allene central carbon at 203 ppm. This was very exciting information and it certainly convinced us that an allene was the impurity inhibiting the Ni-catalyzed hydroboration reaction. Moreover, it is known that cyclization of an allene and an olefin happens simultaneously in the presence of nickel (0).[76] This would consume the nickel catalyst and shut down the desired Ni-catalyzed hydroboration. Accordingly, the origin of the allene impurity was studied. An NMR experiment indicated that hydroboration of enyne **2.132** with $HBCy_2$ was not quite regioselective (6:1) and gave **2.133a** as major isomer which undergoes transmetalations to furnish vinylzinc **2.134a** (Scheme 2.23). It was considered that the minor regioisomer **2.133b** would afford vinylzinc **2.134b**; subsequent allylation with aldehyde **2.128** would give allene **2.137**. Not surprisingly, diene **2.130** and allene **2.137** have extremely similar physical properties and their separation would be challenging.

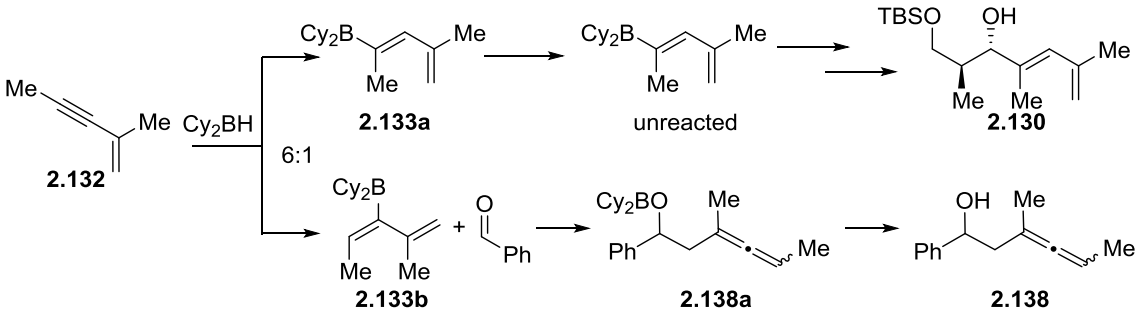
[76] Noucti, N. N.; Alexanian, E. J. *Angew. Chem. Int. Ed.* **2013**, *52,* 8424.

Scheme 2.23. Origin of Allene Impurity



This problematic step was solved by treating the mixture of regioisomers (**2.133a** and **2.133b**) with a surrogate benzylaldehyde prior to B to Zn transmetalation. Only undesired isomer **2.133b** reacted with benzylaldehyde providing allene **2.138** and leaving desired regioisomer **2.133a** untouched (Scheme 2.24). Subsequent transformations of **2.133a** provided **2.130** as sole compound; silica gel chromatography was efficient at separation due to the polarity difference of **2.130** and **2.138**. As an aside, it was also very interesting to find that allene **2.138** was isolated as single diastereomer but its relative stereochemistry was not assigned.

Scheme 2.24. Removal of Allene Impurity

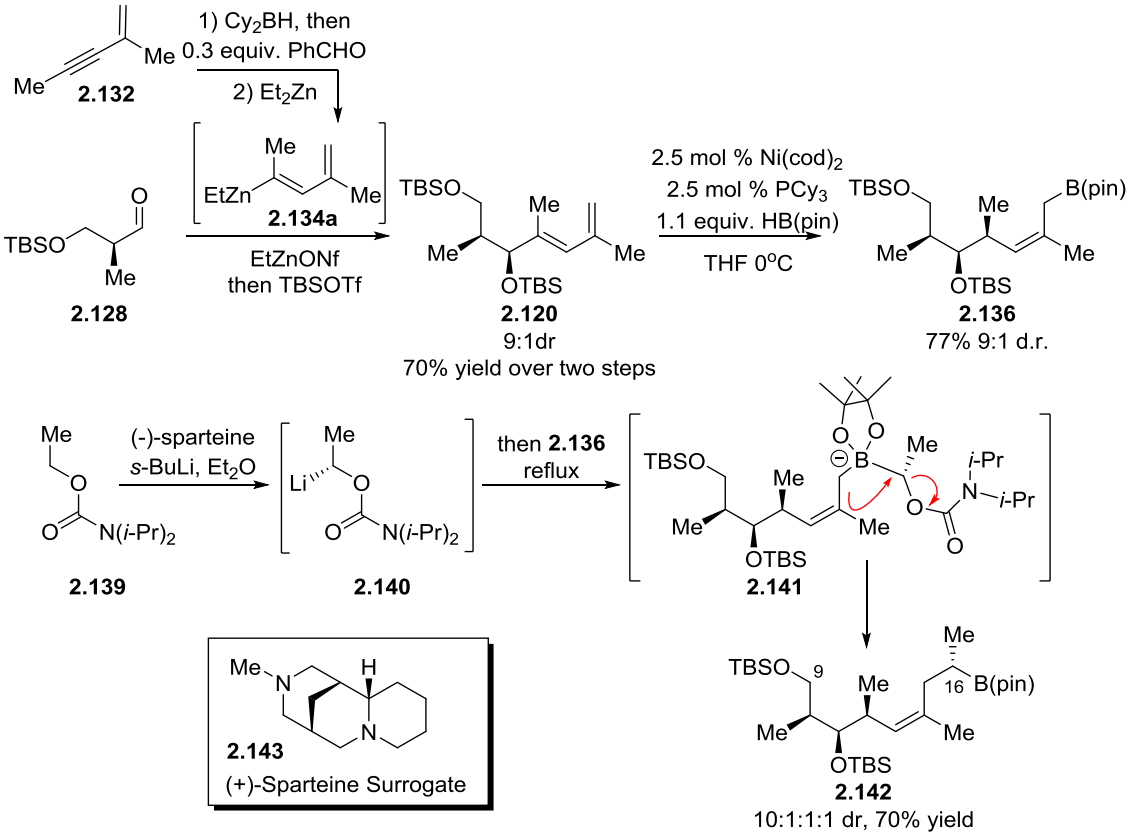


After removal of the allene byproduct, dienol ether **2.120** now participated in Ni-catalyzed hydroboration reaction furnishing (*Z*)-trisubstituted allylboronic acid pinacol ester **2.136** with good yield and diastereoselectivity (Scheme 2.25). Conversion of **2.136**

to **2.142** was accomplished using Hoppe type[77] lithiated ethylcarbamate **2.140** that served as a carbenoid equivalent to homologate a boronic ester (Chapter 1, section 1.1).[78] Unfortunately, the widely used and commercially available (−)-sparteine would give incorrect epimer at C16, and the desired enantiomeric auxiliary is not commercially available. This problem can be solved by using (+)-sparteine surrogate **2.143**, developed by O'Brien and co-workers, which can be obtained in a few steps after isolation of (−)-cytisine from commercially available *Laburnum Anagyroides Cytisus* seeds.[79] With (+)-sparteine surrogate **2.143**, the homologation sequence was performed: to the enantiomerically enriched lithium species **2.140** that was prepared *in situ* from ethylcarbamate **2.139** was added allylboronic ester **2.136** furnishing a boronate complex **2.141**, which, upon heating at reflux, underwent 1,2-migration displacing carbamate and delivering the C9-C16 fragment **2.142**. This fragment contained the *anti*/*syn*-stereotriad, adjacent (*Z*)-trisubstitued olefin, as well as an enantiomerically enriched secondary boronic ester that can serve as a functional handle to adjoin with the C17-C24 fragment (Scheme 2.28). Advanced segment **2.142** was synthesized in only 5 steps from commercially available achiral enyne **2.131**.

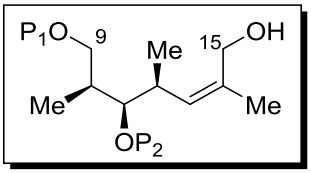
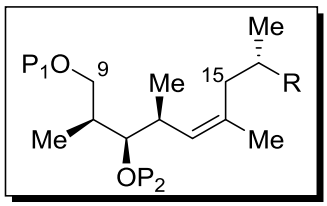
[77] For reviews, see: (a) Hoppe, D.; Christoph, G. Z.; Marek, I. (Eds.), *The Chemistry of Functional Groups Part 1*; Wiley: Chichester **2004**, 1055-1164. (b) Hoppe, D.; Hense, T. *Angew. Chem. Int. Ed*. **1997**, *36*, 2282.
[78] For a review see: Thomas, S. P. T; French, R. M.; Jheengut, V.; Aggarwal, V. K. *The Chemical Record.* **2009**, *9*, 24.
[79] (a) Dearden, M. J.; Firkin, C. R. Hermet, J.-P.; O'Brien, P. *J. Am. Chem. Soc*. **2002**, *124*, 11870. (b) Dixon, A. J.; McGrath, M. J.; O'Brien, P. *Org. Syn*. **2006**, *83*, 141.

Scheme 2.25. Synthesis of the C9-C16 Fragment



Ni-catalyzed diastereoselective hydroboration of chiral 1,3-dienol (Chapter 1) rapidly delivered the C9-C16 fragment **2.142** from a simple hydrocarbon, while similar segments reported in literature were prepared from Roche ester and required more synthetic manipulations (Figure 2.2). Moreover, a methodology described herein enabled accesses to the C9-C16 fragments with different vinyl substituents at C14 position, such as phenyl and silyl substitutions (Chapter 1, table 2.2); thus, it is anticipated that discodermolide analogs with different C14 substitutions can be synthesized, whose biological activities remains underdeveloped.

Figure 2.2. Comparison of C1-C15/C16 Fragments Syntheses

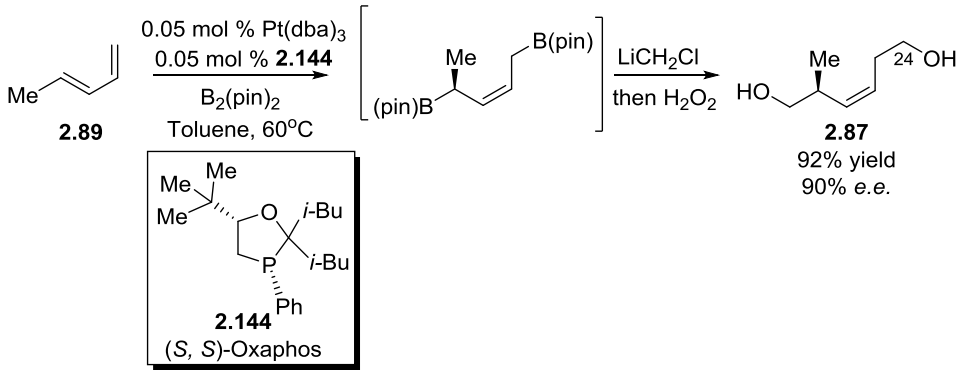
	Schreiber (P_1=P_2=TBS):[18a, 18d] 7 steps from Roche ester, including Roush asymmetric allylation.[80] Myles (P_1=Bn, P_2=TIPS):[18e] 11 steps from Roche ester. Paterson (P_1=PMB, P_2=TBS):[18i] 10 steps from Roche ester, including a Paterson *anti*-aldol reaction.[81] Morken (P_1=P_2=TBS, after in situ oxidation of **2.136**): 4 steps from commercial enyne **2.131**, no auxiliary involved.
	Muzler (P_1=PMB, P_2=TBS, R=CHO):[82] 17 steps from Roche ester, including an Oppolzer sultam[83] based alkylation to install C16 methyl. Morken (P_1=P_2=TBS, R=B(pin)): 5 steps from commercially available enyne **2.131** including a (+)-sparteine surrogate mediated homologation.

2.3.4 Preparation of the C17-C24 Fragment

It was envisioned that the (*Z*)-diene moiety can be synthesized *via* a selective elimination of the relatively less hindered alcohol of 1,6-diol **2.87** (Scheme 2.26). The diol **2.87** was prepared by asymmetric Pt-catalyzed 1,4-diboration of *trans*-pentadiene **2.89** using oxaphos ligand **2.144**[44b] followed by bis-Matteson homologation[45]/oxidation; such single flask reaction produced 1,6-diol **2.87** on multigram scale with good yield and enantioselectivity. With diol **2.87** in hand, selective elimination of the relatively less hindered alcohol at C24 was investigated.

[80] Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc*. **1990**, *112*, 6348.
[81] a) Cowden, C. J.; Paterson, I. *Asymmetric Aldol Reactions using Boron Enolates* in Organic Reactions, Vol. 51 (Ed.: L. A. Paquette), Wiley, New York, 1997, p. 1; b) see ref. 37b
[82] Prantz, K.; Mulzer, J. *Chem.Eur. J*. **2010**, *16*, 485.
[83] Oppolzer, W. *Pure Appl. Chem*. **1990**, *62*, 1241.

Scheme 2.26. Synthesis of 1,6-Diol *via* Pt-Catalyzed Diboration

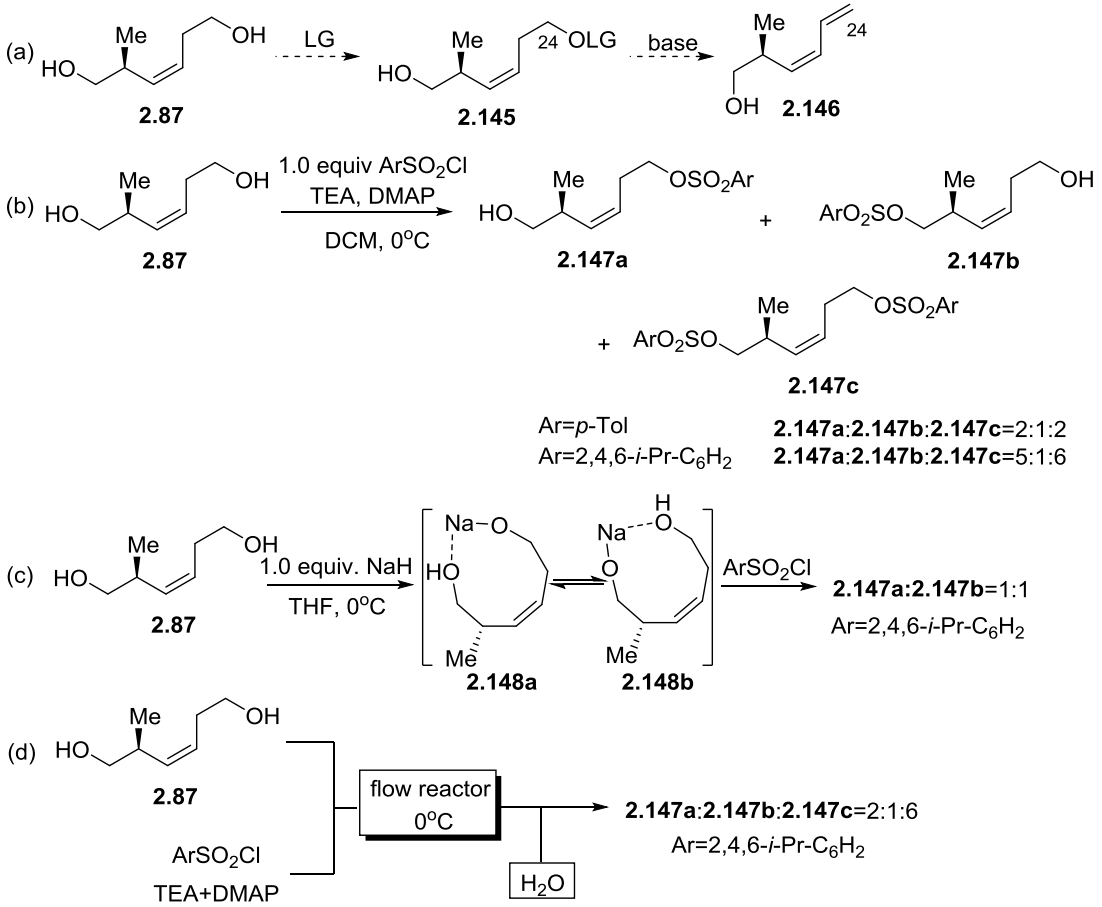


The most efficient strategy would involve installation of an activating group at C24 selectively followed by elimination to afford dienol **2.146** directly (Scheme 2.27a). The first attempt entailed treatment of diol **2.87** with 1.0 equivalent of tosylchloride at 0 ^{o}C; pleasingly, slight regioselectivity was observed preferring desired regioisomer **2.147a** together with an equal amount of bis-tosylate compound **2.147c** (Scheme 2.27b). This result suggested that the relatively less hindered alcohol at C24 did undergo sulfonylation faster. However, after screening various reaction conditions and bases, none of them enhanced regioselectivity and minimized the formation of bis-tosylate **2.147c**. Considering the less sterically demanding tosylchloride might be responsible for the low regioselectivity, more steric hindered sulfonylchloride, 2,4,6-triisopropylbenzene sulfonylchloride, was tested. Under standard reaction conditions, desired regioisomer **2.147a** was formed with synthetically useful levels of selectivity comparing to tosylate (5:1 vs. 2:1), but minimization of bis-sulfonylated product **2.147c** remained unimproved (Scheme 2.27b). Inspired by mono-silylation of a diol reported by McDougal and co-workers,[84] similar strategy was employed. Thus, after deprotonation of 1,6-diol **2.87** with 1.0 equivalent NaH, the heterogeneous solution of alkoxide **2.148** was treated with 2,4,6-

[84] McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. *J. Org. Chem*. **1986**, *51*, 3388.

triisopropylbenzene sulfonylchloride to furnish mono-sulfonylated products (**2.147a** and **2.147b**) exclusively but with only 1:1 regioselectivity (Scheme 2.27c). It is well-documented that continuous flow chemistry could improve batch reaction selectivity;[85] thus the sulfonylation reaction was carried out in a flow reactor to minimize bis-sulfonylate **2.147c** and enhance regioselectivity for **2.147a**. Unfortunately, flow reaction system gave no improvement after several condition optimizations. (Scheme 2.27d).

Scheme 2.27. Selective Sulfonylation of 1,6-Diol



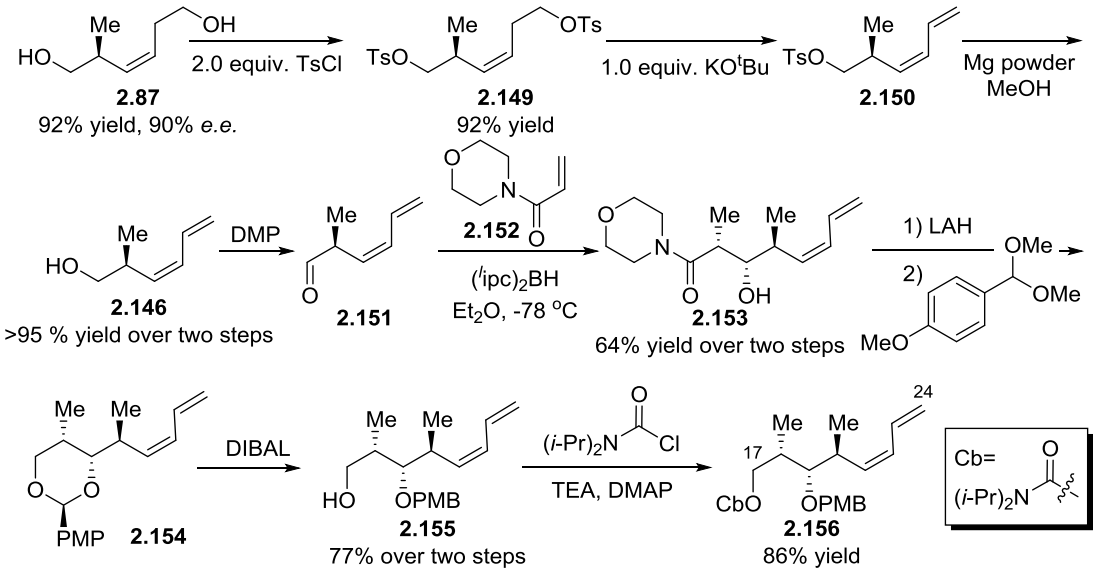
[85] For recent general reviews on continuous flow chemistry, see: (a) Wirth, T. *Microreactors in organic synthesis and catalysis*; Wiley-VCH: Weinheim, 2008. (b) Hartman, R. L.; Jensen, K. F. *Lab Chip* **2009**, *9*, 2495. (c) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev*. **2007**, *107*, 2300. (d) Geyer, K.; Gustafsson, T.; Seeberger, P. H. *Synlett* **2009**, 2382. (e) Kirschning, A.; Solodenko, W.; Mennecke, K. *Chem.;Eur. J*. **2006**, *12*, 5972. (f) Wiles, C.; Watts, P. Eur. *J. Org. Chem*. **2008**, *10*, 1655. (g) Ley, S. V.; Baxendale, I. R. *Proc. Bosen Symp. Syst. Chem*. **2008**, 65. (h) Jahnisch, K.; Hessel, V.; Lowe, H.; Baerns, M. *Angew. Chem. Int. Ed*. **2004**, *43*, 406.

Since mono-activation of diol **2.87** was challenging, a three-step sequence was employed to synthesize dienol **2.150**. After bis-tosylation of diol **2.87** with 2.0 equivalents of TsCl, **2.149** underwent selective elimination with 1.0 equivalent of a sterically hindered base, such as KO*t*-Bu, furnishing (*Z*)-diene **2.150** (Scheme 2.28). Kornblum oxidation[86] was examined to convert tosylate **2.150** to aldehyde **2.151** in one step, but diene isomerization always dominated due to harsh reaction conditions.[57] Therefore, a two-step strategy was used to synthesize dienal **2.151**: removal of tosyl group (**2.150**) with magnesium powder in dry methanol followed by Dess-Martin oxidation of product alcohol **2.146**. Aldehyde **2.151** was subject to reductive aldol reaction with acryloymorpholine **2.152**[87] providing *syn*/*anti*-stereotriad **2.153** as a single diastereomer, and this is the only aldol-type reaction used in the synthesis of (+)-discodermolide. Though the Evans aldol reaction with aldehyde **2.151** was also effective furnishing *syn*/*anti*-stereotriad (61% yield over two steps, single diastereomer), the advantage of Roush reductive aldol reaction is that the morpholine amide moiety in product **2.153** is equivalent to a Weinreb amide in ketone synthesis,[88] which facilitates further transformations (Scheme 2.32). Subsequent $LiAlH_4$ reduction of amide **2.153** to a 1,3-diol, protection as acetal **2.154**, followed by selectively acetal ring opening with DIBAL[89] furnished primary alcohol **2.155** in good yield over three steps. Conversion of alcohol **2.155** to diisopropylcarbarmate **2.156** set the stage to test the key step, a 1,2-migration strategy between lithiated **2.156** and secondary boronic ester **2.142** constructing C16-C17 bond (Scheme 2.13). Overall, the synthesis of C17-C24 (*Z*)-diene

[86] Kornblum, N,; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc*. **1959**, *81*, 4113.
[87] Nuhant, P.; Allais, C.; Roush, W. R. *Angew. Chem. Int. Ed.* **2013**, *52*, 8703.
[88] Martín, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett.* **1997**, *12*, 1414.
[89] Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.

fragment was accomplished in 10 steps from simple *trans*-pentadiene without using Roche ester.

Scheme 2.28. Synthesis of C17-C24 Fragment



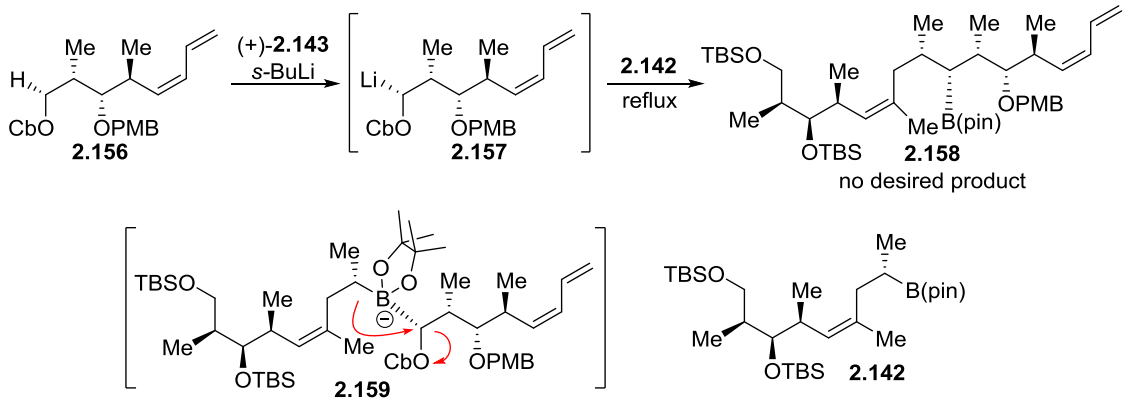
2.3.5. C16-C17 Bond Formation *via* Homologation Strategy

Similar to the homologation strategy used in Scheme 2.25, stereoselective Aggarwal homologation was examined for joining carbamate **2.156** and boronic ester **2.142**. Enantioselective deprotonation of **2.156** should give lithium species **2.157** which would coordinate to boronic ester **2.142** providing a boronate complex **2.159**. It was anticipated that the boronate intermediate would undergo 1,2-migration upon heating, thereby furnishing **2.158** (Scheme 2.29). The proposed fragment union strategy requires that allylboronic ester **2.136** perform two homologations with **2.140** and **2.157** sequentially in a single flask operation.[90] This would transfer boron from **2.136** to

[90] For examples of similar strategies in total synthesis, see: (a) Rasappan, R.; Aggarwal.V. K. *Nature Chem*. **2014**, *6*, 810. (b) Pulis, A. P.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2012**, *134,* 7570. (c) Dutheuil, G.; Webster, M. P.; Worthington, P. A.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2009**, *48*, 6317. (d) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2007**, *46*, 7491.

product **2.158**. Unfortunately, no desired product **2.158** was observed after extensive reaction condition screening, such as addition of Lewis acid to promote 1,2-boronate migration,[91] changing diamine to achiral TMEDA,[92] switching to a better leaving group instead of carbamate,[93] and *in situ* generation of organolithium species preventing potential decomposition.

Scheme 2.29. Construction of C16-C17 Bond

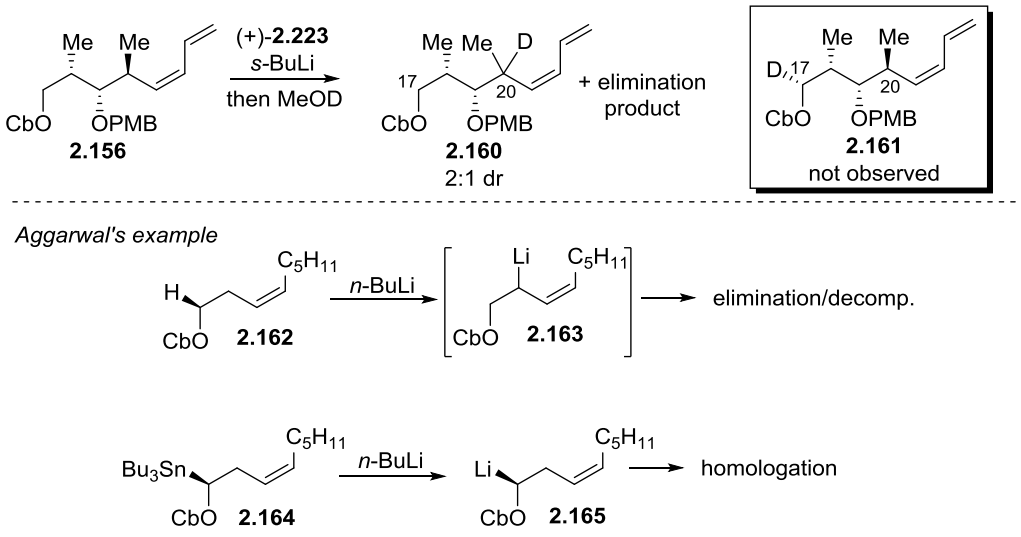


To analyze the problem, the enantioselective deprotonation was studied to find out whether the first step of the homologation sequence works. Carbamate **2.156** was subject to standard deprotonation condition, and MeOD was then used to quench any generated carbon anion (Scheme 2.30). Instead of introducing deuterium at expected carbinol C17 position (**2.161**), surprisingly, deuterium was installed at allylic C20 position (**2.160**). Thus, direct deprotonation of carbamate resulted in substantial deprotonation at allylic position, which was also observed by Aggarwal and co-workers

[91] (a) Pulis, A. P.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2012**, *134*, 7570. (b) Stymiest, J. L.; Dutheuil, G.; Mahmood, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed*. **2007**, *46*, 7491. (c) Tsai, D. J. S.; Jesthi, P. K.; Matteson, D. S. *J. Am. Chem. Soc.* **1983**, *105*, 2077.
[92] Alexander P. Pulis, Philipp Fackler, Varinder K. Aggarwal. *Angew. Chem. Int. Ed.* **2014**, *126*, 4471.
[93] Larouche-Gauthier, R.; Fletcher, C. J.; Couto, I.; Aggarwal, V. K. *Chem. Commun.* **2011**, *47*, 12592.

with compound **2.162** (Scheme 2.30).[94] They solved this problem by introducing a chiral α-hydroxylstannane **2.164**, which gave required organolithium species **2.165** by Li-Sn exchange; this avoids challenging deprotonation in the presence of allylic protons. Though a few attempts to use a similar strategy on diene **2.156** were made, we didn't pursue it any further because it significantly increased the number of steps in the synthesis also incorporated toxic organotin compounds making the synthesis less appealing. Except for the Aggarwal homologation, several strategies were also evaluated to unite these two fragments (**2.156** and **2.142**). For example, transmetalation from enantiomerically enriched boronic ester **2.142** to magnesium [95] or zinc [96] with stereoretention would furnish an organometalic nucleophile, which could add to an aldehyde prepared by oxidation of **2.155** (Scheme 2.28). Unfortunately, no success was achieved for this transmetalation strategy. It looks quite challenging to connect the two fragments at C16-C17 bond. Thus, the synthesis was redesigned.

Scheme 2.30. Unexpected Allylic Deprotonation

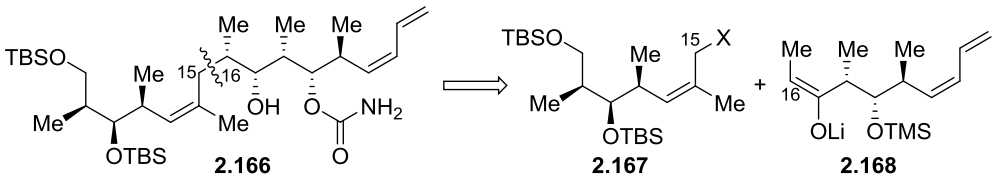


[94] Robinson, A.; Aggarwal, V. K. *Org. Biomol. Chem*. **2012**, *10*, 1795.
[95] Reichle, M. A.; Breit, B. *Angew. Chem. Int. Ed*. **2012**, *51*, 5730.
[96] Hupe, E.; Calaza, M. I.; Knochel, P. *J. Organometallic Chem*. **2003**, *680*, 136.

2.3.6. Revised Fragments Union and Completion of the Synthesis

Instead of breaking C16-C17 bond in (+)-discodermolide, an enolate alkylation was considered to establish C15-C16 linkage between an allyl electrophile **2.242** and enolate **2.243**, both of which can be prepared without significantly changing existed fragments (Scheme 2.31). Similar bond construction *via* enolate alkylation in previous syntheses of discodermolide have employed (*Z*)-enolates that engaged in chelation with the β-oxygen at C19 (Scheme 2.2 and 2.3); these reactions proceeded in moderate selectivity (6:1 dr) and required an excess of precious electrophile **2.167** (2.0 equivalents). It would be of great value and importance to develop a methodology to improve this long-standing problem.

Scheme 2.31. Revised Retrosynthetic Analysis



Inspired by the *anti*-aldol reactions where an α-chiral (*E*)-enolate controls the outcome of α'-position using A(1,3) strain,[97] we considered an α'-alkylation of non-chelated α-chiral (*E*)-enolate. In line with established strategies for acyclic conformational analysis,[98] it was considered that the (*E*)-enolate **2.170** derived from ethyl ketone **2.169**, in the absence of any chelation effects between neighboring functional groups and the metal enolate, might favor conformer **2.170a** such that

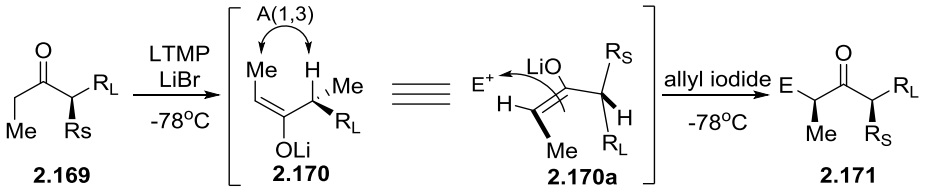
[97] (a) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121. (b) Evans, D. A.; Ng, H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron Lett.* **1992**, *48*, 2127. (c) Paterson, I.; Wallace, D. J.; Velázquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083. (d) For a review, see: Cowden, C. J.; Paterson, I. *Organic Reactions* **1997**, *51*, 1-200.

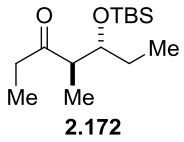
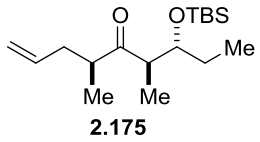
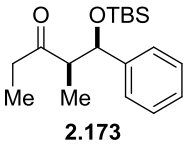
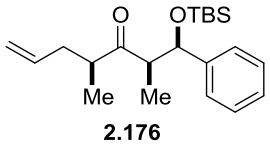
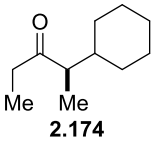
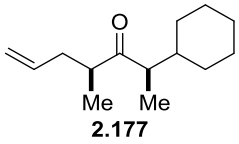
[98] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of organic compounds,* Ed. J. Wiley & Sons, **1994**.

alkylation occurs preferentially from the less hindered *Re* face furnishing product **2.171** (Table 2.2). A preliminary experiment was carried out to test this proposal, and pleasingly, alkylation product **2.175** was formed with high yield and diastereoselectivity by treating (*E*)-enolate (which was generated by ethyl ketone deprotonation with lithium tetramethyl-piperidide (LTMP) in the presence of LiBr[99]) with allyl iodide at low temperature (Table 2.2, entry 1). Of vital importance for eventual scale-up of complex fragment couplings, the reaction yield was excellent as well as diastereoselectivity even when a 1:1 stoichiometry of enolate:electrophile was employed. Furthermore, ketones with adjacent *syn*- and *anti*-propionate moiety (**2.172** and **2.173**) gave desired products (**2.175** and **2.176**) with good yield and selectivity (Table 2.2, entry 1 and 2). Even simple hydrocarbon derived ethyl ketone **2.174** can exhibit useful levels of selectivity and good yield (Table 2.2, entry 3).

[99] Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113,* 9571.

Table 2.2. Diastereoselective (*E*)-Enolate Alkylation[a]

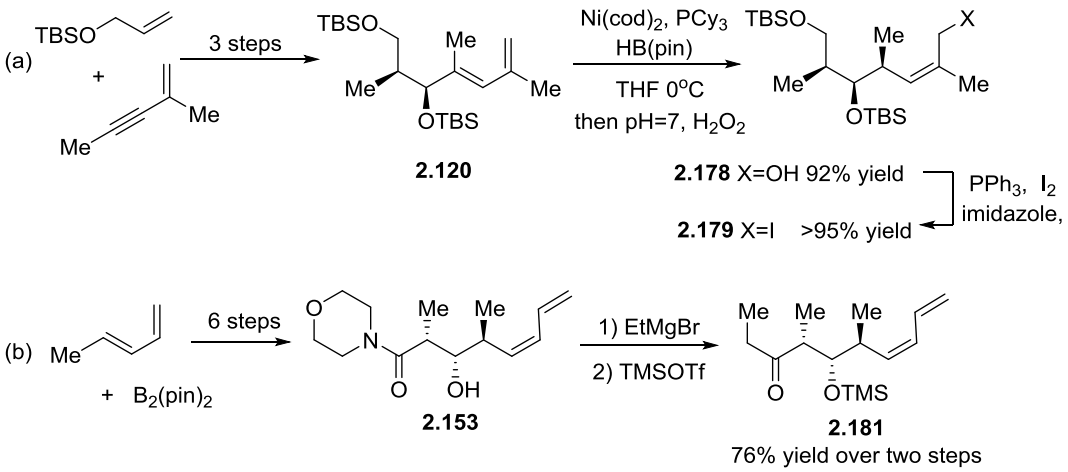


entry	substrate	product	d.r.[b]	yield (%)
1	 **2.172**	 **2.175**	6:1	85
2	 **2.173**	 **2.176**	7:1	92
3	 **2.174**	 **2.177**	3:1	74

[a] LTMP and LiBr were generated *in situ* with 1.0 equivalent of TMP·HBr and 1.95 equiv. *n*-BuLi. [b] dr was determined by ^{1}H NMR.

With diastereoselective enolate alkylation methodology in place, construction of (+)-discodermolide commenced. Desired allyl iodide **2.179** was readily available from iodinolysis of allyl alcohol **2.178** obtained by oxidation of allylboronic ester **2.136** after Ni-catalyzed hydroboration of chiral dienol **2.120** (Scheme 2.32a); ethyl ketone **2.181** was prepared by direct alkylation[88] of reductive aldol product morpholine amide **2.153** furnishing a ketoalcohol that was protected as non-chelating trimethylsilylether (**2.181**) (Scheme 2.32b). Both fragments were rapidly synthesized from readily available achiral hydrocarbons by catalytic stereoselective borylation reactions.

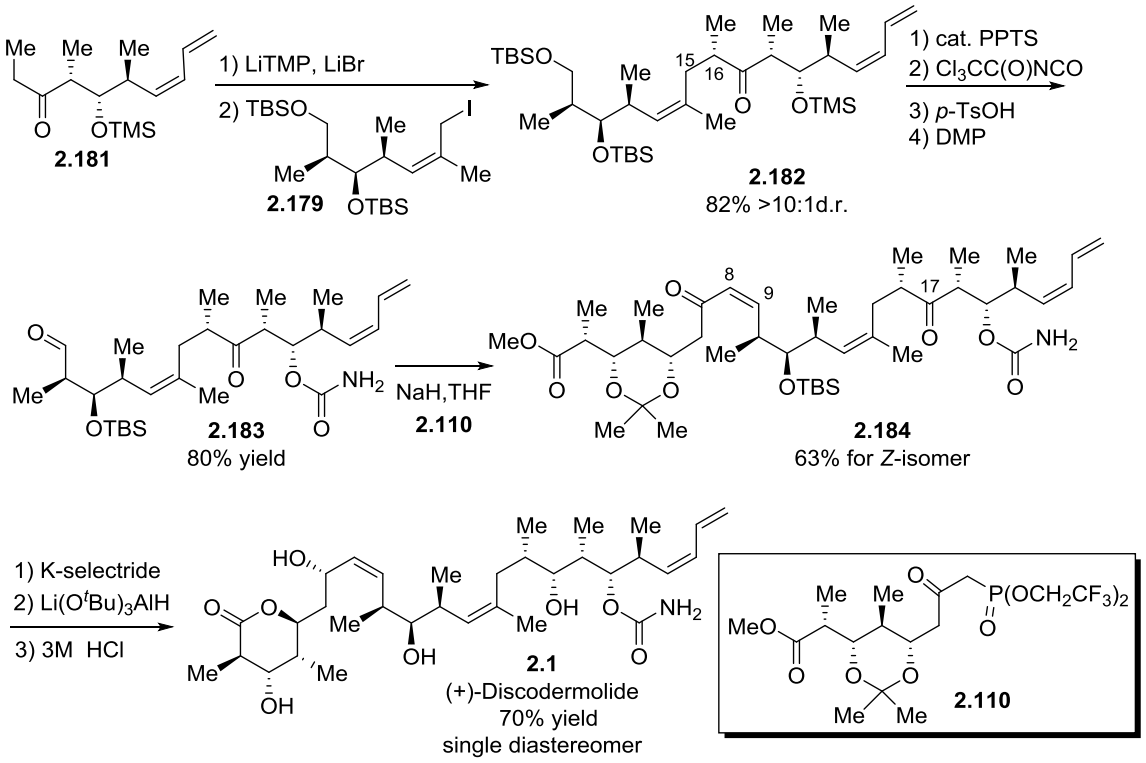
Scheme 2.32. Revised Fragments Syntheses



In line with enolate alkylation reactions described above (Table 2.2), the (*E*)-enolate derived from **2.181** was treated with 1.0 equivalent of allyl iodide **2.179** furnishing **2.182** with excellent yield and diastereoselectivity (Scheme 2.33). After selective removal of the TMS protecting group and installation of requisite carbamate functionality, the primary TBS-protecting group was removed and the product alcohol was oxidized by Dess-Martin periodinane furnishing aldehyde **2.183**. Similar to the Paterson third generation synthesis, a late stage Still-Gennari olefination[19] was employed between the aldehyde **2.183** and phosphonate **2.110** to provide the full carbon skeleton (**2.184**) of (+)-discodermolide in good yield. The less hindered α,β-unsaturated ketone at C7 was selectively reduced with K-Selectride® at −78 °C in high diastereoselectivity, and it was suggested by Paterson and co-workers that the high diastereoselectivity was controlled by the conformational preference of C1-C6 region in the presence of cyclic moiety (C3-C5 acetonide).[100] Then, a chelation controlled reduction of the crude mono-ketone at C17 with LiAl(O*t*-Bu)$_3$H gave an intermediate diol, which was treated with aqueous HCl for deprotective lactonization to complete the (+)-discodermolide synthesis.

[100] Paterson, I.; Lyothier, I. *J. Org. Chem*. **2005**, *70*, 5494.

Scheme 2.33. Fragments Union and Completion of the Synthesis



Overall, (+)-discodermolide was synthesized in a total of 36 steps with the longest linear sequence of 17 steps (13% overall yield) from commercially available achiral hydrocarbons.

2.4. Progress toward Synthesis of Oxidation-Resistant Analog

The potential therapeutic applications and unique biological activities of (+)-discodermolide have driven a number of research programs toward the design, synthesis, and evaluation of its analogs. After disclosure of discodermolide's undesired pulmonary toxicity in early phase clinical trials by Novartis,[101] it became more important to find an analog that was less toxic while maintaining cytotoxicity.[102] Up to date, hundreds of

[101] Longley, R. E. Discodermolide: past, present, and future. *Natural Products and Cancer Drug Discovery*. Springer New York, **2013**, p 39-58.
[102] For a review see: Smith, A. B. III; Freeze, B. S. *Tetrahedron*, **2008**, *64*, 261. For selected recent discodermolide analogue synthesis, see: (a) Lemos, E. L; Agouridas, E.; Sorin, G.;

discodermolide analogs were prepared and studied, and such a huge analog library helps scientists understand the drug's structure activity relationship (SAR). For example, it was proved that the C8-C9 (*Z*)-olefin as well as C13-C14 region are critical to maintain potent cell growth inhibition activity.[103] Perturbation of the C11 and C17 hydroxyl groups is detrimental to discodermolide biological activity.[104] On the other hand, some significant changes to discodermolide structure are well-tolerated. For instance, the carbarmate and the C23-C24 olefin can be completely removed or appended with various substitutions, while maintaining cell growth inhibitory activity.[18d] The lactone C1-C7 region could be simplified without losing significant potency.[105]

Further studies on metabolism of discodermolide revealed that nearly complete oxidation occurred in one hour after treatment with human liver microsomes; oxidation happened largely around electronically enriched C13-C14 trisubstituted olefin area, such as allylic oxidation and dihydroxylation.[106] However, it is unknown whether the pulmonary toxicity alluded to above arises from discodermolide itself or from metabolic byproducts. Thus it is reasonable to conclude that synthesis of analogs targeting a C13-C14 trisubstituted olefin might render more oxidation-resistant and even more potent drug candidates. However, limited analogs have been prepared and studied to probe the C13-C14 substitution for SAR (Figure 2.3). Both Schreiber and Smith/Kosan Bioscience

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Guerreiro, A.; Commerçon, A.; Pancrazi, A.; Betzer, J.-F.; Lannou, M.-I.; Ardisson, J. *Chem. Eur. J.* **2011**, *17*, 10123. b) Paterson, I.; Naylor, G. J.; Gardner, N.M.; Guzman, E.; Wright, A. E. *Chem. Asian J*. **2011**, *6*, 459 c) Paterson, I.; Naylor, G. J.; Fujita, T.; Guzman, E.; Wright, A. E. *Chem. Commun*. **2010**, *46*, 261 d) Fan, Y.; Schreiber, E. M.; Day, B. W. *J. Nat. Prod.* **2009**, *72*, 1748.

[103] Gunasekera, S. P.; Longley, R. E.; Isbrucker, R. A. *J. Nat. Prod*. **2002**, *65*, 1830.

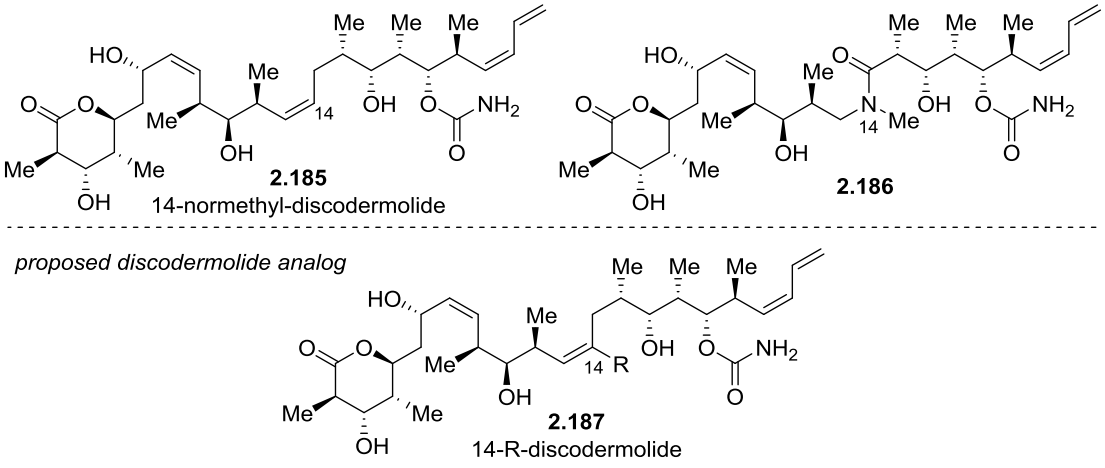
[104] (a) Gunasekera, S. P.; Longley, R. E.; Isbrucker, R. A. *J. Nat. Prod*. **2001**, *64*, 171; (b) Isbrucker, R. A.; Gunasekera, S. P.; Longley, R. E. *Cancer Chemother. Pharmacol*. **2001**, *48*, 29.

[105] Shaw, S. J.; Sundermann, K. F.; Burlingame, M. A.; Myles, D. C.; Freeze, B. S.; Xian, M.; Brouard, I.; Smith, A. B., III. *J. Am. Chem. Soc*. **2005**, *127,* 6532.

[106] Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. *Mol. Pharmacol.* **1997**, *52*, 613.

synthesized 14-normethyl-discodermolide **2.185**, which showed little impact on inhibitory potency. Novartis introduced an *N*-methyl amide (**2.186**) which was intended to mimic the C13-C15 trisubstituted olefin; this resulted in significant loss in the drug's potency. These are the only two designed examples of trisubstituted (*Z*)-olefin variations in literature, and it was suspected that the lack of examples may be attributed to the difficulties in trisubstituted (*Z*)-olefin synthesis (Scheme 2.11).[6] It was anticipated that our synthetic approach together with novel borylation strategies developed for (+)-discodermolide synthesis will offer access to new discodermolide analogs (**2.187**) that may address biological limitations of the natural product itself.

Figure 2.3. Synthetic Analogs of C13-C15 Variants



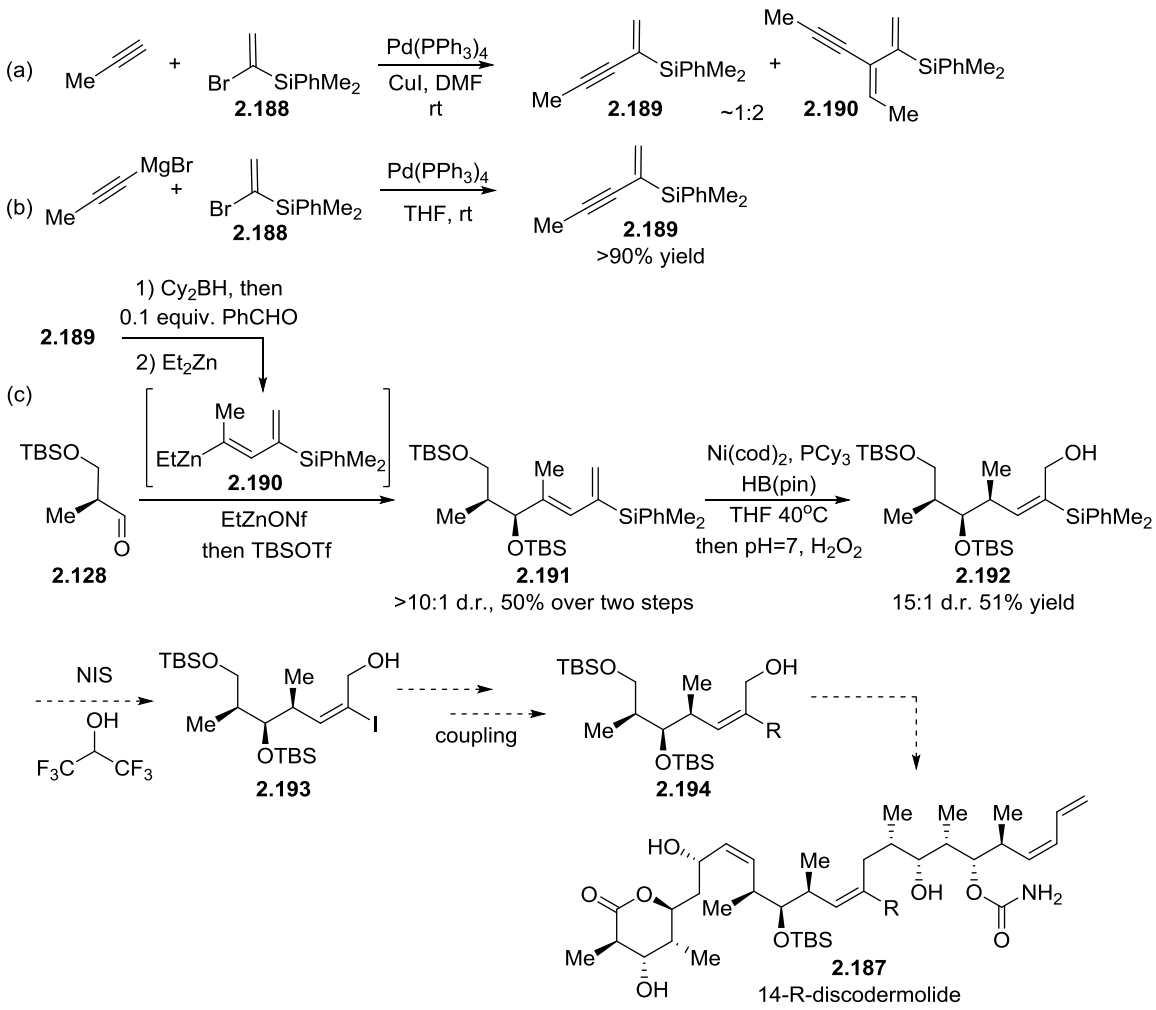
It was considered that a Ni-catalyzed hydroboration/oxidation sequence, applied to a silicon-substituted (*Z*)-allylic alcohol (Chapter 1, Table 1.2), would provide a vinyl silane that can be converted to various substitutions (Chapter 1). In line with the synthesis of chiral dienol ether **2.120** (Scheme 2.25), it is necessary to prepare silicon substituted 1,3-enyne **2.189** for diene synthesis. The initial attempts employed Sonogashira

coupling[107] of vinylbromide **2.188** and excess propyne. Unfortunately, byproduct **2.190** was obtained as major compound, which was inseparable from desired **2.289** by silica gel chromatography (Scheme 2.34a). The byproduct **2.190** might arise from hydro-propynation of **2.189** [108] or from carbopalladation of 2,4-hexadiyne (from propyne dimerization) with vinylpalladium derived from vinyl bromide **2.188**. [109] A new methodology was developed to address this problem: Kumada[110] type sp-sp^2 coupling was accomplished between premetalated propyne and vinylbromide **2.188** at room temperature, furnishing enyne **2.189** cleanly in excellent yield (Scheme 2.34b). With enyne **2.189** in hand, a reaction sequence of hydroboration, boron to zinc transmetalation, and chelation controlled addition to aldehyde **2.128** gave a dienol and the product alcohol was protected as TBS-ether to afford desired chiral dienol **2.191** with good diastereoselectivity (Scheme 2.34c). Pleasingly, diene **2.191** participated in Ni-catalyzed hydroboration reaction providing (*Z*)-allylic alcohol **2.192** with good diastereoselectivity and moderate/unoptimized yield. Utilizing conditions developed by Zakarian and Holton,[111] the (*Z*)-vinyl silane **2.192** can be stereoselectively converted to (*Z*)-vinyl iodide **2.193**, which can participate in various cross coupling reactions to install different functional groups at C14 vinyl position (**2.194**). Further transformations, including (*E*)-enolate alkylation and Still-Gennari olefination,[19] would provide discodermolide analogs

[107] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467.
[108] Vollhardt, K. C.; Winn, L. *Tetrahedron Lett.* **1985**, *26*, 709.
[109] (a) Suzenet, F.; Parrain, J. L.; Quintard, J. P. *Eur. J. Org. Chem*. **1999**, *11*, 29572. (b) For carbometalation see, Knochel, P. "*Carbometallation of Alkenes and Alkynes*" in Comprehensive Organic Synthesis (Eds.: Trost, B. M.; Fleming, I.) Pergamon Press, Oxford, 1991, vol. 4, p. 865-911.
[110] (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc*. **1972**, *94*, 4374. (b) Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun*. **1972**, *144*.
[111] (a) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822. (b) Lu, C. D.; Zakarian, A. *Org. Lett*. **2007**, *6*, 3161. (c) Ilardi, E. A.; Stivala, C. E.; Zakarian, A. *Org. Lett.* **2008**, *10*, 1727.

2.187 with different substitution at C14, which haven't been systemically synthesized and studied previously.

Scheme 2.34. Synthesis of C9-C15 Trisubstituted Vinyl Silane Fragment

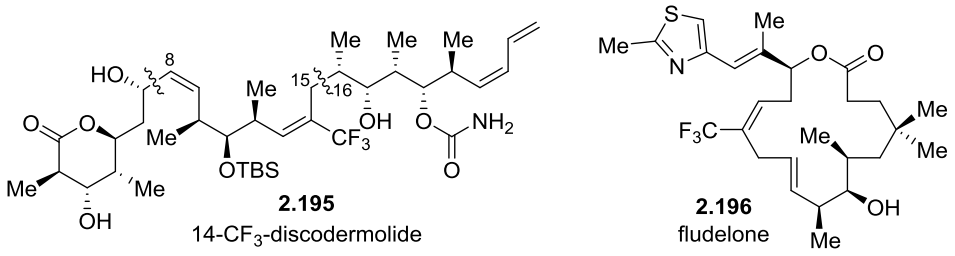


Another important but challenging analog candidate is 14-CF_3-discodermolide **2.195**, which is sterically similar to discodermolide (Figure 2.4); however, the fluorine atoms can greatly affect natural products' metabolic stability.[112] For example, the presence of fluorine substitutions has rendered 26-trifluoro-epothilone B (fludelone) **2.196** with increased drug stability toward oxidation and enhanced activity in treating

[112] Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3.

xenograft tumors in nude mice; this was synthesized and studied by Danishefsky and co-workers.[113] Thus, it is reasonable to consider a 14-trifluoromethyl discodermolide as an oxidation-resistant analog toward metabolic degradation, which might resolve the undesired pulmonary toxicity. Retrosynthetic analysis of **2.195** is quite similar to that used for (+)-discodermolide (Scheme 2.13 and Scheme 2.31), disconnecting the molecule to three equally complex fragments.

Figure 2.4. Trifluoromethyl Substitued Discodermolide and Fludelone



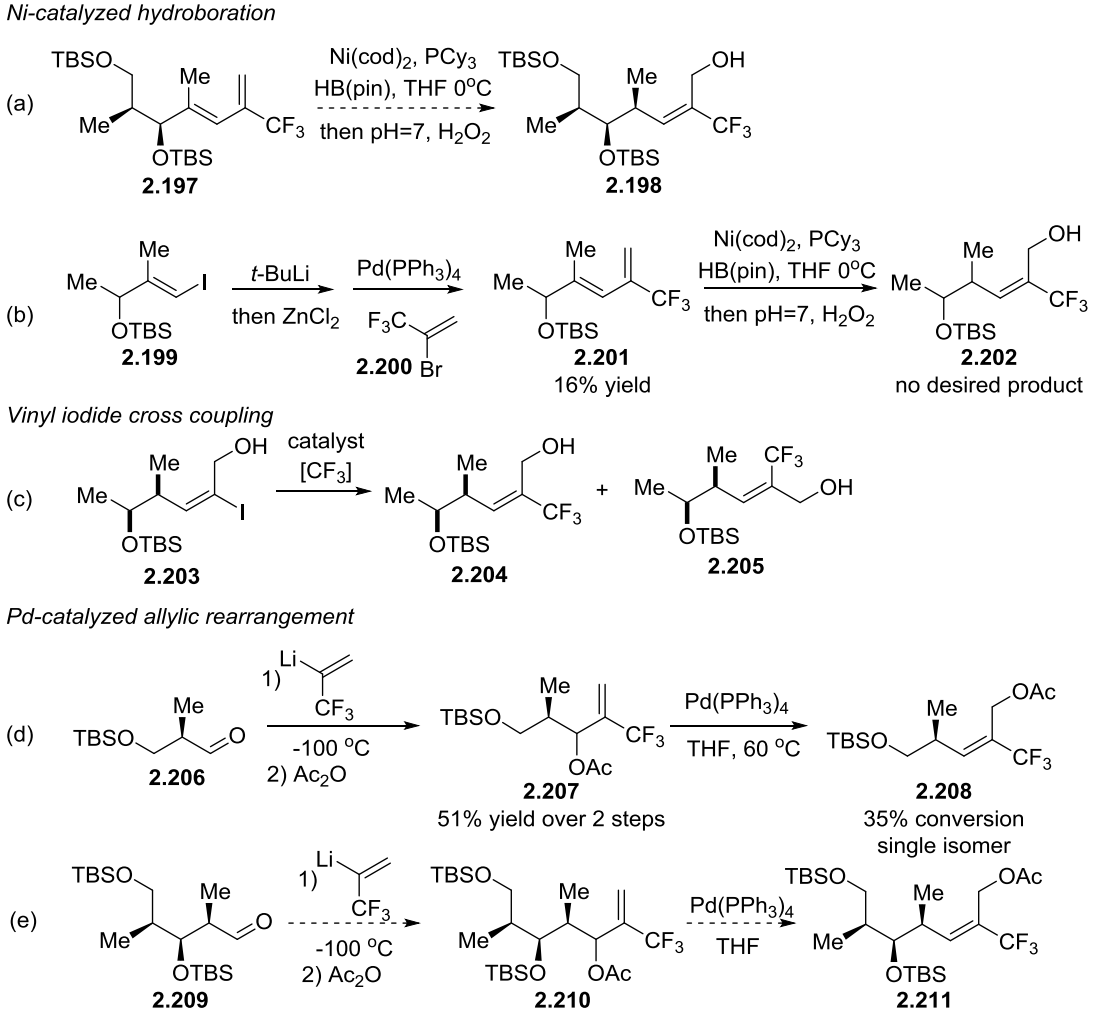
It is important to synthesize the central fragment **2.198** bearing a (*E*)-CF_3-substituted olefin. The first thought was to directly apply Ni-catalyzed hydroboration onto a trifluoromethyl-substituted diene **2.197** (Scheme 2.35a). After a number of attempts, Negishi cross coupling[114] of commercially available vinyl bromide **2.200** and vinyl zinc derived from vinyl iodide **2.199** was found to be the only effective method to synthesize the model substrate **2.201** (Scheme 2.35b). Diene **2.201** was subjected to the standard Ni-catalyzed hydroboration conditions, but no desired product **2.202** was isolated. Another possibility to prepare **2.202** is using cross coupling method[115] to convert vinyl iodide (**2.203**) (available from corresponding vinylsilane, Scheme 2.34) to vinyl-

[113] Chou, T. C.; Dong, H. J.; Rivkin, A.; Yoshimura, F.; Gabarda, A. E.; Cho, Y. S.; Tong, W. P.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 4762.
[114] (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) E. Negishi in Aspects of Mechanism and Organometallic Chemistry, Plenum, New York, 1978, pp. 285-317.
[115] (a) Hafnera, A.; Brase, S. *Adv. Synth. Catal*. **2011**, *353*, 3044. (b) Urata, H. Fuchikamp, T. *Tetrahedron Lett.* **1991**, *32*, 91.

trifluoromethyl substituent (**2.204**) (Scheme 2.35c). However, both electrophilic and nucleophilic methods[116] for this transformation gave an isomerized mixture of (*Z*)- and (*E*)-olefins (**2.204** and **2.205**) in low yield or no conversion at all. Developed by Iseki and co-workers, a Pd-catalyzed allylic rearrangement of vinyl trifluoromethyl-substituted allyl-acetate generating highly (*E*)-selective product was considered.[117] This method was first tested on a model substrate **2.207**, which was prepared by addition of a vinyllithium to aldehyde **2.128** followed by acetate protection of the product alcohol (Scheme 2.35d). The model substrate **2.207** was subjected to Pd-catalyzed allylic rearrangement conditions and, pleasingly, (*E*)-allyl-acetate **2.208** was isolated with excellent stereoselectivity. Thus we believe that the desired C9-C15 fragment **2.211** can be synthesized by employing similar strategy on readily accessible acetate **2.210** (Scheme 2.35e).

[116] For a review, see: Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem. Int. Ed*. **2013**, *52*, 8214.
[117] (a) Iseki, K.; Kuroki, Y.; Nagai, T.; Kobayashi, Y. *J. Fluorine Chem*, **1994**, *69*, 5. (b) Iseki, K.; Kuroki, Y.; Nagai, T.; Kobayashi, Y. *Chem. Pharm. Bull.* **1996**, *44*, 477.

Scheme 2.35. Synthesis of Vinyl-Trifluoromethyl Substituted C9-C15 Fragment



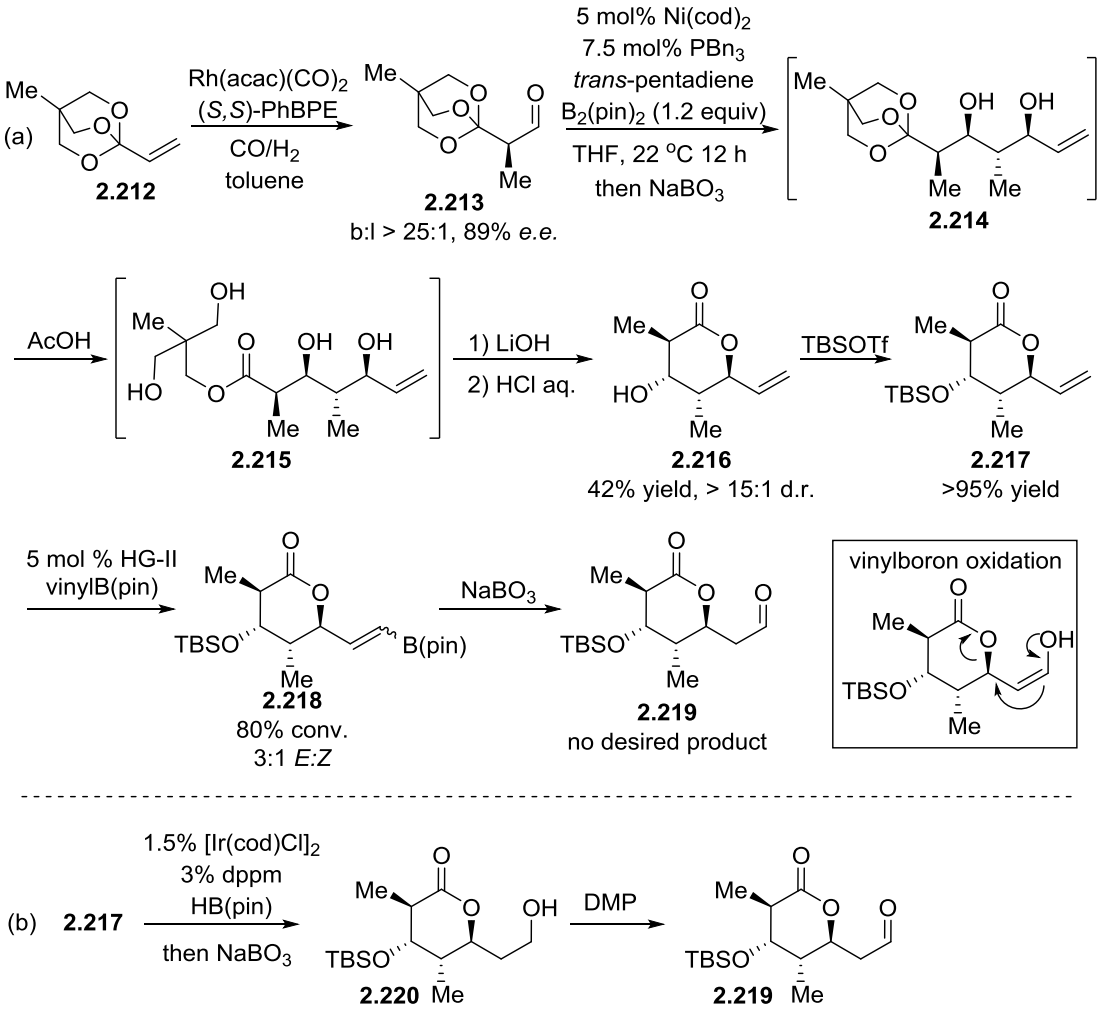
With previous experience in synthesizing C1-C9 fragment (Scheme 2.16), a more concise sequence is employed to construct the δ-lactone (Scheme 2.36a). Orthoester derived aldehyde **2.213** (available from asymmetric hydroformylation of olefin **2.212**)[118] participated in Ni-catalyzed borylative diene-aldehyde coupling reaction furnishing intermediate 1,3-diol **2.214**. Subsequent orthoester ring opening under acidic conditions followed by lactonization provided **2.216** with good yield and excellent diastereo-selectivity. This single-flask transformation directly built-up the challenging fully

[118] For similar asymmetric hydroformylation, see: Risi, R. M.; Burke, S. D. *Org. Lett*. **2012**, *14*, 2572.

substituted δ-lactone **2.216** bearing a terminal olefin for further functionalization. After TBS-protection of the alcohol, **2.217** underwent cross metathesis[119] with vinyl boronic ester providing an intermediate vinyl boron **2.218** with 3:1 *E:Z* ratio. The next step was proposed as its *in situ* oxidation directly furnishing aldehyde **2.219**. However, only a trace amount of desired aldehyde **2.219** was isolated, which might due to the concomitant lactone ring opening during vinyl boron oxidation. This can be addressed by a two-step sequence (Scheme 2.36b): Ir-catalyzed hydroboration/oxidation sequence of terminal olefin **2.217**[51] followed by Dess-Martin periodinane oxidation of alcohol **2.220** gave aldehyde **2.219**. The aldehyde **2.219** is not stable on silica gel chromatography,[100] and was used for next step without further purification.

[119] Overview of cross metathesis: (a) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243. (b) Prunet, J.; Grimaud, L. *In Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*; Cossy, J., Arseniyadis, S., Meyer, C., Eds; VCH-Wiley: Weinheim, 2010; p 287.

Scheme 2.36. Synthesis of C1-C7 δ-Lactone Fragment

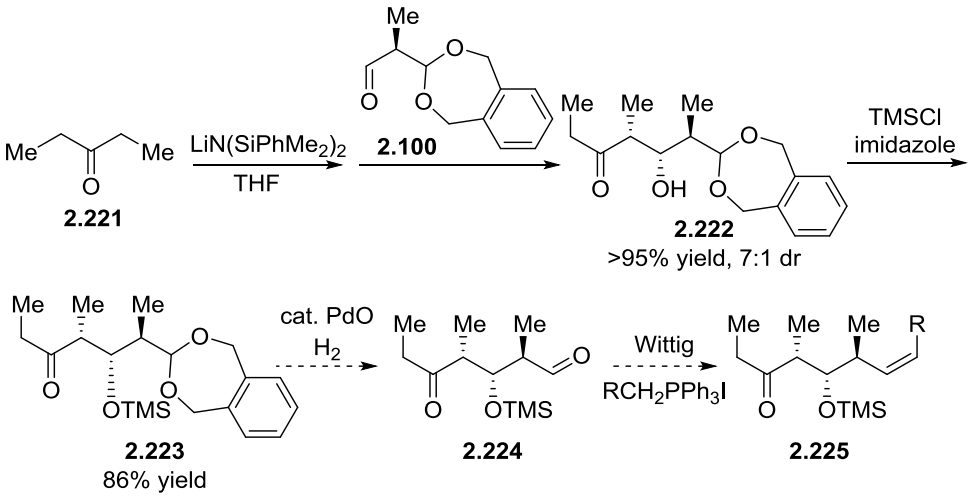


Ethyl ketone segment **2.181** could be simplified as **2.225** since the C23-C24 terminal olefin of the diene is not biologically important.[18d] Thus a much shorter and more efficient route to ethyl ketone **2.225** was examed (Scheme 2.37). A *syn*-aldol condensation between 3-pentanone **2.221** and asymmetric hydroformylation product aldehyde **2.100** gave ethyl ketone **2.222** with excellent yield and good diastereo-selectivity *via* chelation controlled process.[120] It is worth pointing out that this one step reaction constructed not only the stereotriad moiety but also a masked aldehyde motif

[120] Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**,*104*. 5526.

that could be further functionalized to requisite *cis*-olefin. After installation of a non-chaleting trimethylsilyl protecting group for future (*E*)-enolate alkylation, the *o*-xylyl acetal (**2.223**) can be removed under neutral conditions.[48] Unfortunately, all attempts to isolate the product ketoaldehyde **2.224** failed, which might attribute to its rapid decomposition after removing the acetal protection (trace **2.224** was detected in crude ^{1}H NMR). Protection of the ketone moiety may render a more stable product aldehyde and subsequent Wittig olefination/deprotection would afford desired ethyl ketone **2.225** setting the stage for the diastereoselective (*E*)-enolate alkylation.

Scheme 2.37. Synthesis of C16-C24 Ethyl Ketone

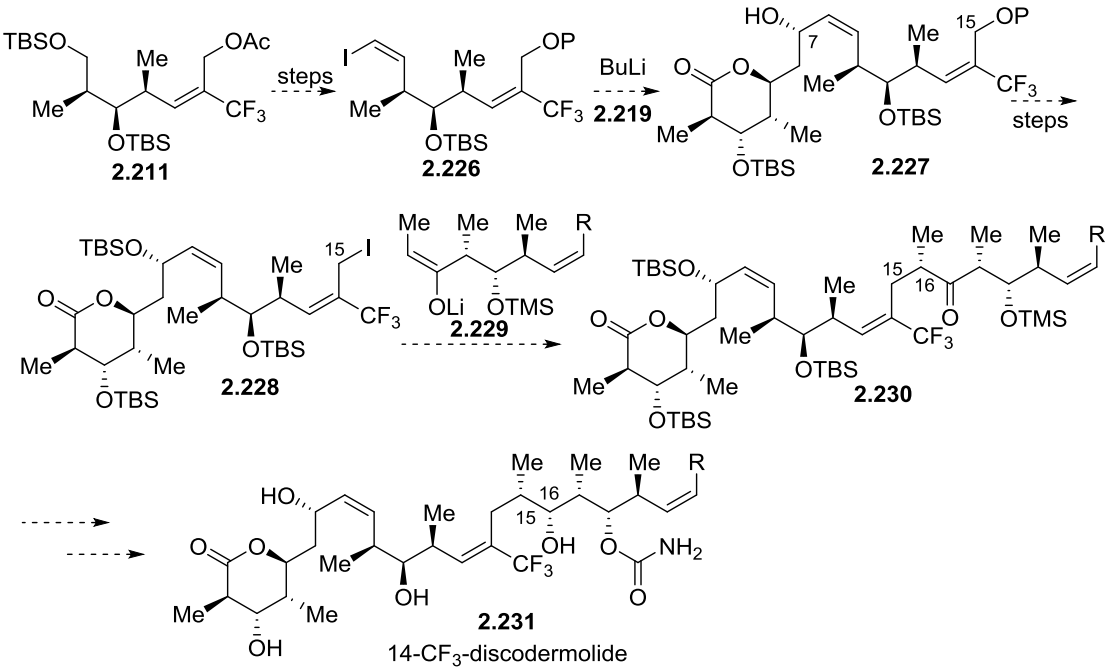


Cis-vinyl iodide **2.226** can be prepared *via* Stork-Wittig olefination[26] with the aldehyde derived from **2.211**. Then, addition of **2.226**-derived vinylmetal reagent to aldehyde **2.219** would provide **2.227** furnishing the left-half of the molecule (Scheme 2.38). If the addition reaction is not diastereoselective, an oxidation/CBS reduction[121] sequence would establish correct stereochemistry at C7.[122] After converting **2.227** to allyl

[121] (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, E. J. Helal, C. J. *Angew. Chem. Int. Ed*. **1998**, *37*, 1986.
[122] For similar strategy in synthesis of discodermolide, see: ref. 18q

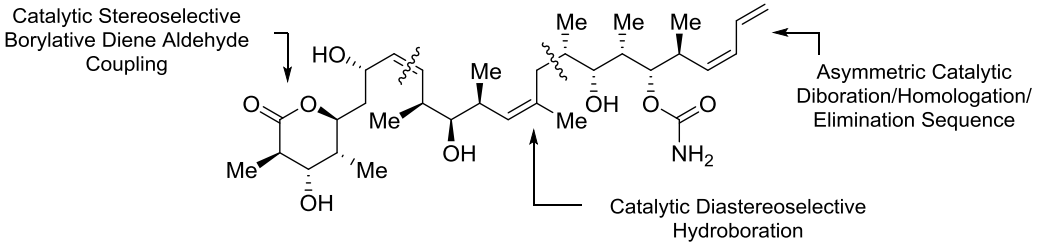
iodide **2.228**, a late-stage alkylation with ethyl ketone **2.225**-derived (*E*)-enolate **2.229** would construct C15-C16 bond (**2.230**). Finally, subsequent transformations would complete the synthesis of 14-CF_3-discodermolide **2.231**.

Scheme 2.38. Proposed Endgame of 14-CF_3-Discodermolide



2.5 Conclusion

Figure 2.5. Summary of Total Synthesis of (+)-Discodermolide



In conclusion, the total synthesis of (+)-discodermolide was completed with a longest linear sequence of 17 steps (total 36 steps) in 13% overall yield from commercially available achiral hydrocarbons. Three advanced fragments were rapidly constructed by catalytic stereoselective borylation reactions that were developed in our

laboratory, and the fragment union was accomplished by the Still-Gennari olefination and a novel diastereoselective (*E*)-enolate alkylation. Taking advantage of the asymmetric hydroformylation of terminal olefins (Chapter 3), our approach also features the first Roche ester-free discodermolide synthesis. Furthermore, Roush reductive *syn*-aldol reaction was the only aldol type reaction used in the synthesis of this complex polyketide natural product. Most importantly, the synthetic strategy enabled preparation of challenging discodermolide analogs targeting a C13-C14 trisubstituted (*Z*)-olefin. It is also anticipated that oxidation-resistant analog **2.231** with increased *in vivo* stability may address biological limitations of the natural product itself. With the successful preparation of advanced intermediates and model substrate study, we believe that our synthetic route could provide challenging 14-CF_3-discodermolide **2.231** in the near future and, hopefully, it would exhibit good biological activity serving as a promising drug candidate.

2.6. Experimental Procedures

General Information

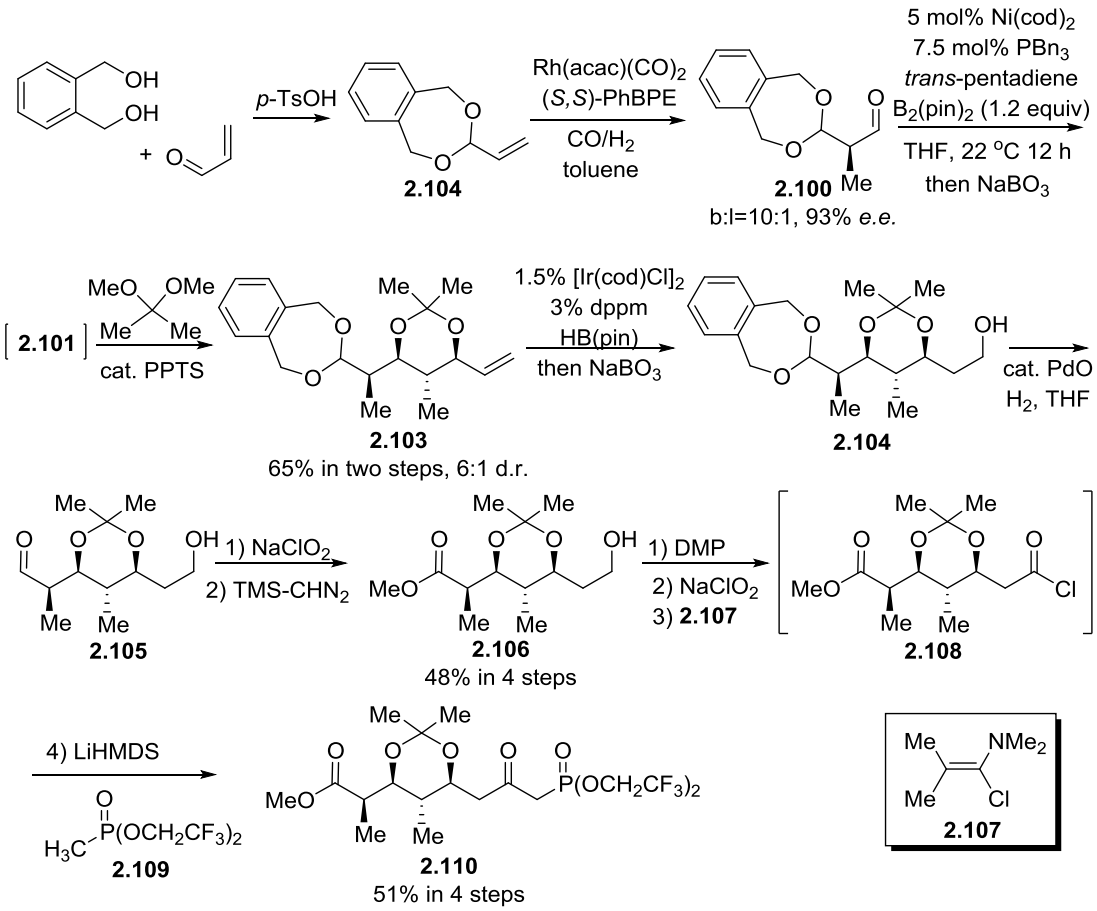
^{1}H NMR spectra were recorded on either a Varian Gemini-400 (400 MHz), or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts were reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm, C_6D_6: 7.16 ppm). Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on either a Varian Gemini-400 (100 MHz), or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.23 ppm). Infrwered (IR) spectra were recorded on a Bruker alpha spectrophotometer, ν_{max} cm^{-1}. Bands were characterized as broad (br), strong (s), medium (m), and weak (w). High resolution mass spectrometry was performed at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 40-63 μm) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid (PMA) in ethanol, potassium permanganate ($KMnO_4$) in water, or cerium (IV) sulfate and ammonium molybdate in sulfuric acid (CAM). Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Chromatograph equipped with an auto

sampler and a Waters photodiode array detector with isopropanol as the modifier. Analytical chiral high-performance liquid chromatography (HPLC) was performed on a Agilent 1120 liquid chromatograph equipped with a UV detector and Chiraclpak-AD-H column or Chiraclpak-AS-H column. Hydroformylation was performed in an Argonaut Technologies Endeavor® Catalyst Screening System using 1:1 H_2/CO supplied by Airgas, Inc.

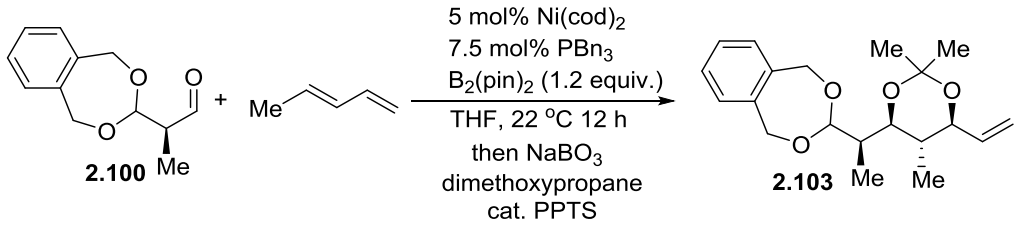
All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF), dichloromethane (CH_2Cl_2), and diethyl ether were purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. Bis(pinacolato)diboron was obtained from AllyChem Co., Ltd. and recrystallized from pentane prior to use. Pinacol borane was obtained from BASF. Bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$), dicarbonylacetylacetonato rhodium (I) ($Rh(acac)(CO)_2$), palladium oxide, bis(1,5-cyclooctadiene)diiridium(I) dichloride $[Ir(cod)Cl]_2$ and phosphine ligands were purchased from Strem Chemicals, Inc. and used without further purification. *trans*-1,3-Pentadiene was purchased from ChemSampCo. Dess-Martin periodinane was purchased from Oakwood Products Inc. 2-methylpent-1-en-3-yne is obtained from Acros Organics, allyl iodide is from Lancaster Chemicals. All other reagents were purchased from either Fisher or Aldrich and used without further purification.

I. C1-C8 Fragment (Scheme 2.16)



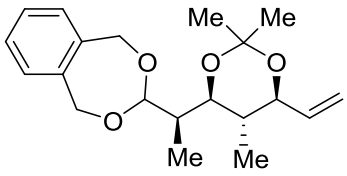
For the preparation of terminal olefin **2.104** and aldehyde **2.100** see Chapter 3.

Procedure for Borylative Diene Aldehyde Coupling



An oven-dried 20 mL scintillation vial, equipped with a magnetic stir-bar, was charged with $Ni(cod)_2$ (24.0 mg, 0.087 mmol), PBn_3 (39.6.mg, 0.131 mmol), and THF (6.0 mL) in a dry box under an argon atmosphere. After stirring for 5 min, the aldehyde

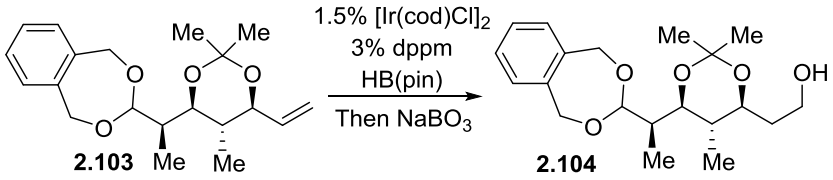
2.100 (from asymmetric hydroformylation and used directly without further purification.) (360 mg, 1.74 mmol), *trans*-1,3-pentadiene (132 mg, 1.92 mmol) and $B_2(pin)_2$ (531 mg, 2.1 mmol) were added sequentially. The vial was sealed with a polypropylene cap and removed from the dry box. The reaction mixture was allowed to stir at ambient temperature for 14 h. After this time, the mixture was poured into 100 mL round bottom flask with $NaBO_3$ (870 mg, 8.7 mmol) and water (6.0 mL). The mixture was allowed to stir at ambient temperature for 20 h. The resulting mixture was diluted with water and the two-phase mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was evaporated *in vacuo*. The residue was passed through a pad of Celite with ethylacetate and evaporated *in vacuo*. The crude material was re-dissolved in 1,1-dimethoxypropane (1.0 mL) and catalytic amount of PPTS was added. Such mixture was stirred at room temperature until TLC showed full consumption of 1,3-diol (occasionally removal of methanol was necessary in order to achieve full conversion). The reaction mixture was concentrated and purified by silica gel chromatography to afford the titled compound as colorless oil (375 mg, 65% over two steps, 6:1 d.r.) R_f = 0.55 (ethyl acetate: hexanes=1:4, stain in $KMnO_4$).



3-((*R*)-1-((4*S*,5*S*,6*S*)-2,2,5-Trimethyl-6-vinyl-1,3-dioxan-4-yl)ethyl)-1,5-dihydrobenzo[e][1,3]dioxepine (Scheme 2.16, 2.103). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23-7.17 (4H, m), 5.76 (1H, ddd, *J* =17.5, 10.5, 8.0 Hz), 5.27 (1H, d, *J* = 17.5 Hz), 5.22 (1H, dd, *J* = 10.5, 1.5 Hz), 4.88 (4H, d, *J* = 5.5 Hz), 4.79 (1H, d, *J* =8.0 Hz), 3.97 (1H, dd, *J* =11.0,

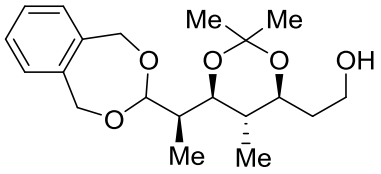
2.0 Hz), 3.92 (1H, dd, J = 10.0, 7.5 Hz), 1.98 (1H, qdd, J = 6.0, 6.0, 2.0 Hz), 1.49 (3H, s), 1.50-1.48 (1H, m, overlap), 1.41 (3H, s), 0.99 (3H, d, J = 6.0 Hz), 0.70 (3H, d, J = 6.0Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.7, 139.6, 137.6, 127.7, 127.6, 118.3, 110.2, 98.2, 77.7, 72.7, 72.3, 38.0, 35.0, 30.3, 20.0, 11.6, 8.3; IR (neat): 2988 (w), 2938 (w), 1455 (w), 1378 (m), 1254 (m), 1201 (m), 1121 (s), 1042 (s), 938 (m), 738 (m); HRMS-(ESI+) for $C_{20}H_{28}O_4Na$ $[M+Na]^+$: calculated: 355.1880, found: 355.2873. $[\alpha]_D^{21}$ = +22.219 (c = 0.64, $CHCl_3$, l = 50 mm).

Procedure for Hydroboration of Terminal Olefin[51]



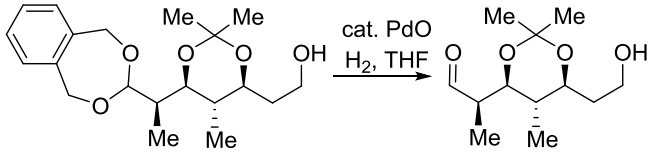
A flame dried 50 mL round-bottom flask was charged with $[Ir(cod)Cl]_2$ (12 mg, 0.008 mmol) and dppm (14 mg, 0.016 mmol) in glove box. CH_2Cl_2 (7.0 mL), pinacolborane (344 mg, 2.7 mmol), and alkene **2.103** (750 mg, 2.26 mmol) were added successively at room temperature. The flask was sealed and brought out of box. The mixture was then stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. THF (5.0 mL), water (5.0 mL) and $NaBO_3$ (1.13 g, 11.3 mmol) were added to the residue and was stirred for 10 h at room temperature. The resulting mixture was diluted with water and the two-phase mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the titled

compound **2.104** as colorless oil (560 mg, 71%). R_f = 0.31 (ethyl acetate: hexanes=1:2, stain in $KMnO_4$).



2-((4*S*,5*S*,6*S*)-6-((*R*)-1-(1,5-Dihydrobenzo-[e][1,3]dioxepin-3-yl)ethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)ethan-1-ol (Scheme 2.16, 2.104). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23-7.17 (4H, m), 4.88 (4H, d, *J* = 8.5 Hz), 4.77 (1H, d, *J* = 8.5 Hz), 3.94 (1H, dd, *J* = 10.0, 2.0 Hz), 3.82-3.74 (3H, m), 2.83 (1H, br, s), 1.99-1.90 (2H, m), 1.72-1.69 (1H, m), 1.57 (1H, ddq, *J* = 10.0, 10.0, 7.0 Hz), 1.47 (3H, s), 1.38 (3H, s), 0.99 (3H, d , *J* = 7.0 Hz), 0.71 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7, 127.8, 127.6, 110.2, 98.2, 76.2, 72.8, 72.7, 72.4, 61.6, 38.0, 35.2, 35.0, 30.3, 19.9, 11.6, 8.3; IR (neat): 3444 (w), 3091 (m), 2939 (m), 1455 (w), 1397 (s), 1259 (m), 1202 (s), 1122 (s), 1044 (s), 942 (m), 738 (m); HRMS-(ESI+) for $C_{20}H_{31}O_5$ $[M+H]^+$: calculated: 351.2172, found: 351.2178. $[\alpha]_D^{21}$ = +22.829 (*c* = 0.30, $CHCl_3$, *l* = 50 mm).

Procedure for Removal of 1,2-Benzenedimethanol Actal Protecting Group[48]

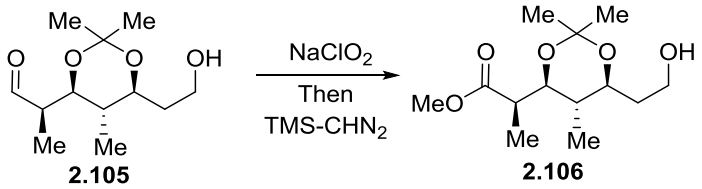


2.104 **2.105**

Dry THF (6.8 mL) was added to a mixture of alcohol **2.104** (240 mg, 0.68 mmol) and PdO (4.2 mg, 0.034 mmol) in 20-dram vial under nitrogen. The vial was purged with a hydrogen balloon and the mixture was stirred under 1 atm of hydrogen until TLC showed full consumption of starting material. Resulting mixture was diluted with diethyl

ether and passed through a pad of Celite with diethyl ether. The aldehyde **2.105** was used directly after concentration for next step without further purification.

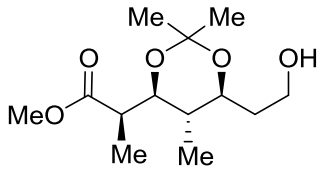
Procedure for Converting Aldehyde to Methyl ester



2.105 **2.106**

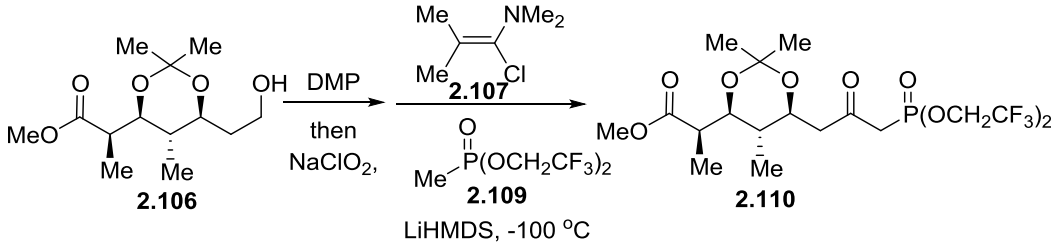
Crude aldehyde **2.105** (max = 0.68 mmol) was dissolved in *t*-BuOH (5.6 mL) and a few drops of 2-methyl-2-butene. A water (5.6 mL) solution of $NaClO_2$ (122 mg, 1.36 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (563 mg, 4.08 mmol) was added dropwise, and the reaction mixture was stirred for 1 h before being partitioned between brine (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude acid was used for next step without any further purification.

Crude acid (max = 0.68 mmol) was dissolved in hexane (6.8 mL) and MeOH (0.68 mL). TMS-CHN_2 (2 M in hexane) was added dropwise at room temperature until the yellow color persisted. The reaction mixture was then stirred for 30 min, quenched with 1 drop of AcOH, and concentrated under reduced pressure. Purification by flash chromatography to afford methyl ester as a colorless oil (140 mg, 80% over three steps). R_f = 0.23 (1:2 hexanes:ethyl acetate, stain in $KMnO_4$)



Methyl-(*R*)-2-((4*S*,5*S*,6*S*)-6-(2-hydroxyethyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoate (Scheme 2.16, 2.106). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.06 (1H, dd, *J* = 15.5, 2.5 Hz), 3.76 (2H, td, *J* = 9.5, 2.0 Hz), 3.72-3.67 (1H, m, overlap), 3,67 (3H, s), 2.73 (1H, br, s), 2.67 (1H, qd, *J* = 7.5, 2.5 Hz), 1.95-1.90 (1H, m), 1.69-1.62 (1H, m), 1.52 (1H, qdd, *J* = 10.0, 10.0, 6.5 Hz), 1.41 (3H, s), 1.31 (3H, s), 1.12 (3H, d, *J* = 7.5 Hz), 0.77 (3H, d, *J* =6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 98.5, 75.4, 74.7, 61.3, 51.9, 41.0, 35.5, 34.9, 30.1, 19.6, 11.8, 8.7; IR (neat): 3428 (w), 2990 (m), 2945 (m), 2882 (m), 1734 (s), 1380 (m), 1255 (m), 1203 (s), 1169 (s), 1142 (s), 1049 (s), 952 (m); HRMS-(ESI+) for $C_{13}H_{24}O_5Na$ $[M+Na]^+$: calculated: 283.1516, found: 283.1516. $[\alpha]_D^{21} = -5.699$ (*c* = 0.50, $CHCl_3$, *l* = 50 mm).

Procedure for Converting Alcohol to β-Ketophosphonate[100]



Alcohol **2.106** (140 mg, 0.54 mmol) was dissolved in CH_2Cl_2 (5 mL). $NaHCO_3$ (544 mg, 6.5 mmol) was added, followed by Dess-Martin periodinane (275 mg, 0.65 mmol). The reaction mixture was stirred for 30 min, and aqueous $Na_2S_2O_3$ was then added. After stirring at room temperature for 15 min, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was evaporated *in vacuo*. Hexane (3 mL) was then added to the residue, and the precipitate was filtered through a

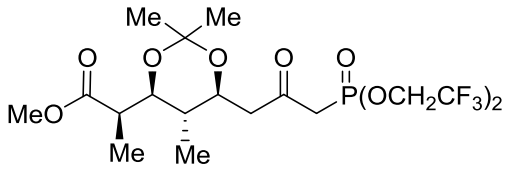
pad of silica and concentrated *in vacuo*. The aldehyde was sufficiently clean and was used for next step without further purification.

Crude aldehyde (max = 0.54 mmol) was dissolved in *t*-BuOH (4.5 mL) and a few drops of 2-methyl-2-butene. A water (4.5 mL) solution of $NaClO_2$ (97 mg, 1.08 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (447 mg, 3.24 mmol) was added dropwise, and the reaction mixture was stirred for 1 h before being partitioned between brine (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was re-extracted with ethylacetate (5 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude acid was used for next step without any further purification.

Carboxylic acid (max = 0.54 mmol) was dissolved in CH_2Cl_2 (6.4 mL). 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine **2.107** (158 mg, 1.20 mmol) was added dropwise and stirred at room temperature for 1 h before being concentrated under reduced pressure. The crude acid chloride **2.108** was dried under high vacuum for 30 min to remove all volatiles (*Crude NMR spectrum of corresponding acid chloride has been attached*). In the meantime, methylphosphonic acid bis(2,2,2-trifluoroethyl) ester **2.109** (458 mg, 1.76 mmol) was dissolved in THF (1.5 mL) and cooled to −98 °C (methanol/liquid nitrogen). LiHMDS (1.0 M in THF, 1.76 mL, 1.76 mmol) was added, and the reaction mixture was stirred at −98 °C for 10 min before the addition of the crude acid chloride **2.108** in solution of THF (3.9 mL). The mixture was stirred for 1 h at −98 °C, quenched with aqueous NH_4Cl (5 mL), and allowed to warm to room temperature. After dilution with water, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried over Na_2SO_4, concentrated under reduced pressure, and purified by

flash chromatography affording β-ketophosphonate **2.110** as a viscous colorless oil (142 mg, 51% over four steps). R_f = 0.50 (1:1 hexanes:ethyl acetate, stain in $KMnO_4$)

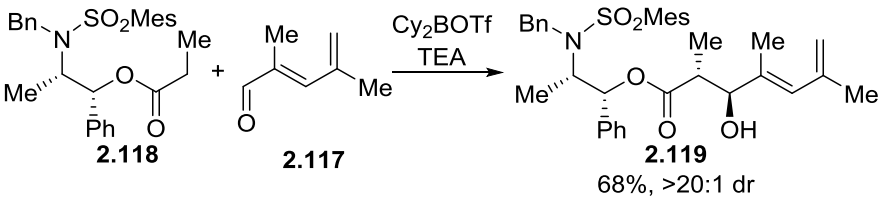
Note: excess methylphosphonic acid bis(2,2,2-trifluoroethyl) ester has exact the same R_f value with product **2.110**, thus making purification extremely hard. But later we found that methylphosphonic acid bis(2,2,2-trifluoroethyl) ester can be removed under vacuum with gentle heating, leaving clean β-ketophosphonate with similar yield.



Methyl-(*R*)-2-((4*S*,5*S*,6*S*)-6-(3-(bis(2,2,2-trifluoroethoxy)phosphoryl)-2-oxopropyl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoate (Scheme 2.16, 2.110). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.44 (4H, qd, *J* = 8.0 Hz), 4.07 (1H, dd, *J* = 10.0, 3.0 Hz), 3.99 (1H, td, *J* = 9.0, 3.0 Hz), 3.68 (3H, s), 3.36 (2H, dd, *J* = 21.0, 2.0 Hz), 2.74 (1H, dd, *J* = 15.0, 3.5 Hz), 2.69-2.64 (2H, m), 1.45 (1H, qd, *J* = 6.5, 4.0 Hz), 1.38 (3H, s), 1.28 (3H, s), 1.12 (3H, d, *J* = 7.0 Hz), 0.77 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.4, 174.8, 98.7, 74.5, 72.0, 62.6 (q), 51.9, 48.0, 43.4, 42.3, 41.0, 35.6, 29.8, 19.4, 11.7, 8.7; IR (neat): 2975 (w), 1724 (m), 1382 (w), 1290 (m), 1258 (m), 1164 (s), 1066 (s), 960 (s), 845 (m), 655 (w); HRMS-(ESI+) for $C_{18}H_{31}F_6NO_8P$ $[M+NH_4]^+$: calculated: 534.1692, found: 534.1691. $[\alpha]_D^{21} = -12.584$ (*c* = 1.34, $CHCl_3$, *l* = 50 mm).

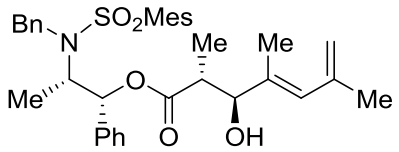
II. C9-C15 Fragment (Scheme 2.18)

i) Synthesis of Chiral Dienol Ether by Abiko-Massamune Aldol Reaction



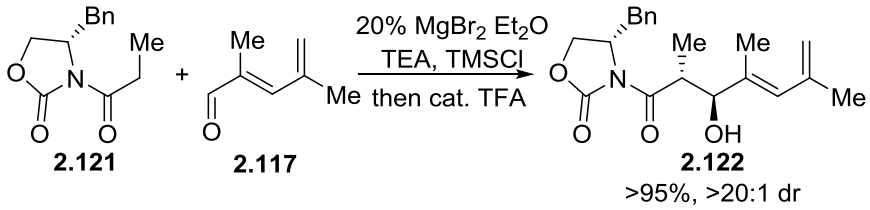
For the preparation of aldehyde **2.117** see Chapter 1.

To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added **2.118** then the flask was purged with N_2. NEt_3 (1.60 mL, 11.50 mmol) and CH_2Cl_2 (24 mL) were then added and the flask was cooled to −78 °C. Cy_2BOTf[58] (5.30 mL of a 2.0 M solution in hexanes, 10.55 mmol) was added dropwise and the reaction was allowed to stir at −78 °C for 30 min. Aldehyde **2.117** (528 mg, 4.80 mmol) was added dropwise and the reaction was allowed to at −78 °C for 30 min then gradually warm to room temperature and stir for 2 h. MeOH (10 mL), pH=7 buffer (10 mL), and 30 *wt* % hydrogen peroxide (5 mL) were then sequentially added and the reaction was allowed to stir for 12 h. The reaction mixture was diluted with ethyl acetate (30 mL) and water (30 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (15:1:1 hexanes:ethyl acetate: CH_2Cl_2) to afford the title compound as a clear, colorless oil (2.10 g, 77%). R_f = 0.20 (15:1:1 hexanes:ethyl acetate: CH_2Cl_2, stain in $KMnO_4$).



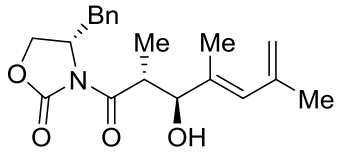
(2*R*,3*S*,*E*)-(1*R*,2*S*)-2-(*N*-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl 3-hydroxy-2,4,6-trimethylhepta-4,6-dienoate (Scheme 2.18, 2.119): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (2H, d, *J* = 8.5 Hz), 7.26-7.17 (6H, m), 6.90 (2H, s), 6.85 (2H, dd, *J* = 8.5 Hz, 1.0 Hz), 5.86 (1H, s), 5.83 (1H, d, *J* = 4.0 Hz), 5.03 (1H, dd, *J* = 1.5 Hz, 1.5 Hz), 4.84 (1H, s), 4.82 (1H, d, *J* = 17.0 Hz), 4.61 (1H, d, *J* = 17.0 Hz), 4.11-4.06 (2H, m), 2.64 (1H, dq, *J* = 14.5 Hz, 7.0 Hz), 2.52 (6H, s), 2.45 (1H, d, *J* = 3.5 Hz), 2.29 (3H, s), 1.85 (3H, s), 1.74 (3H, d, *J* = 1.0 Hz), 1.16 (3H, d, *J* = 7.0 Hz), 0.97 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.8, 142.8, 141.3, 140.5, 139.0, 138.5, 135.5, 133.7, 132.5, 131.4, 128.6, 128.5, 128.1, 127.8, 127.3, 126.0, 116.1, 80.8, 78.5, 57.0, 48.5, 43.7, 23.7, 23.2, 21.1, 14.5, 13.6, 12.5; IR (neat): 3546 (w), 2980 (w), 2939 (w), 1746 (s), 1603 (m), 1453 (m), 1323 (s), 1152 (s), 1018 (m), 698 (m); HRMS-(ESI$^+$) for $C_{35}H_{43}NO_5SNa$ [M+Na]: calculated:612.2760, found: 612.2748.

Synthesis of Chiral Dienol Ether by Evans anti-Aldol Reaction

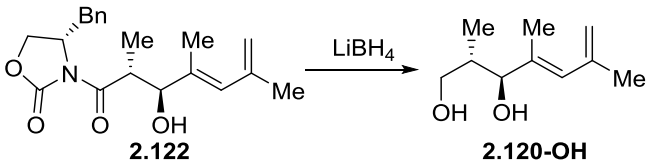


The reaction was following literature procedure.[60] Oxazolidinone **2.121** (1.94 g, 8.3 mmol) was treated with $MgBr_2 \cdot Et_2O$ (430 mg, 1.6 mmol, 0.2 equivalent), triethylamine (1.68 g, 16.6 mmol), chlorotrimethylsilane (1.35 g, 12.5 mmol), aldehyde **2.117** (1.1 g, 10 mmol) in 16.6 mL ethylacetate at room temperature for 24 h. The light yellow slurry was pushed through a plug of silica gel with Et_2O. The reaction mixture

was concentrated *in vacuo*, and methanol was added along with two drops to TFA. This was stirred at room temperature for 30 min and concentrated to a pale yellow oil and passed through a plug of silica gel to afford titled compound **2.122** with almost quantitative yield and can be used for next step without further purification. R_f = 0.27 (2:1 hexanes:ethyl acetate).

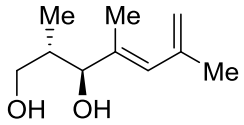


(*S*)-4-Benzyl-3-((2*R*,3*S*,*E*)-3-hydroxy-2,4,6-trimethylhepta-4,6-dienoyl)oxazolidin-2-one (Scheme 2.18, 2.122) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.32 (2H, m), 7.28-7.24 (3H, m), 5.94 (1H, s), 5.03 (1H, s), 4.86 (1H, s), 4.72-4.68 (1H, m), 4.21-4.16 (3H, m, overlap), 3.32 (1H, dd, *J* = 14.0, 3.5 Hz), 2.78 (1H, dd, *J* = 13.5, 9.5 Hz), 1.87 (6H, s, overlap), 1.11 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.8, 154.0, 141.4, 136.2, 135.5, 130.8, 129.7, 129.1, 127.5, 116.0, 81.8, 66.3, 55.8, 40.9, 38.0, 23.7, 15.0, 12.9; IR (neat): 3496 (b), 2973 (w), 1775 (s), 1696 (s), 1454 (w), 1383 (s), 1350 (s), 1250 (m), 1209 (s), 1107 (m), 1011 (s), 895 (m), 761 (m), 702 (s), 509 (m); HRMS-(ESI$^+$) for $C_{20}H_{24}O_3$ [M+H-H_2O]: calculated:326.1756, found: 326.1769. $[\alpha]_D^{21}$ = +71.577 (*c* = 0.84, $CHCl_3$, *l* = 50 mm).

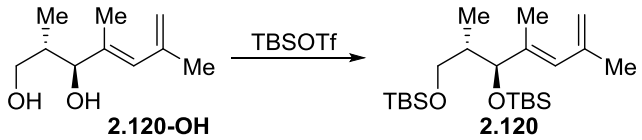


A dry round bottom flask containing a magnetic stir bar was charged with crude **2.122** (~10 mmol), MeOH (0.67 mL, 20 mmol), and THF (100 mL) then sealed with a septum and cooled to 0 °C. Lithium borohydride (8.3 mL of a 2.0 M solution in

tetrahydrofuan, 16.6 mmol) was added dropwise and the reaction was allowed to stir for 1 h. The reaction was quenched with H_2O (20 mL) followed by the addition of saturated potassium sodium tartrate solution (50 mL) and the reaction mixture was allowed to stir for 3 h. The reaction was diluted with EtOAc (30 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by silica gel chromatography (1:1 hexanes:EtOAc) to afford the diol **2.120-OH** as a clear oil (1.10 g, 78%). R_f = 0.34 (1:1 hexanes:ethyl acetate, stain with $KMnO_4$).

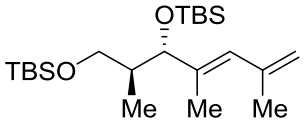


(2*S*,3*S*,*E*)-2,4,6-Trimethylhepta-4,6-diene-1,3-diol (Scheme 2.22, 2.120-OH) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (1H, s), 5.02 (1H, s), 4.85 (1H, s), 3.91 (1H, d, *J* = 8.5 Hz), 3.76-3.65 (1H, m), 1.87 (3H, s), 1.81 (3H, s), 0.76 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.5, 137.7, 130.1, 115.7, 85.1, 68.5, 37.7, 23.8, 14.0, 12.9; HRMS-(ESI+) for $C_{10}H_{19}O_2$ $[M+H]^+$: calculated: 171.1385, found: 171.1385.



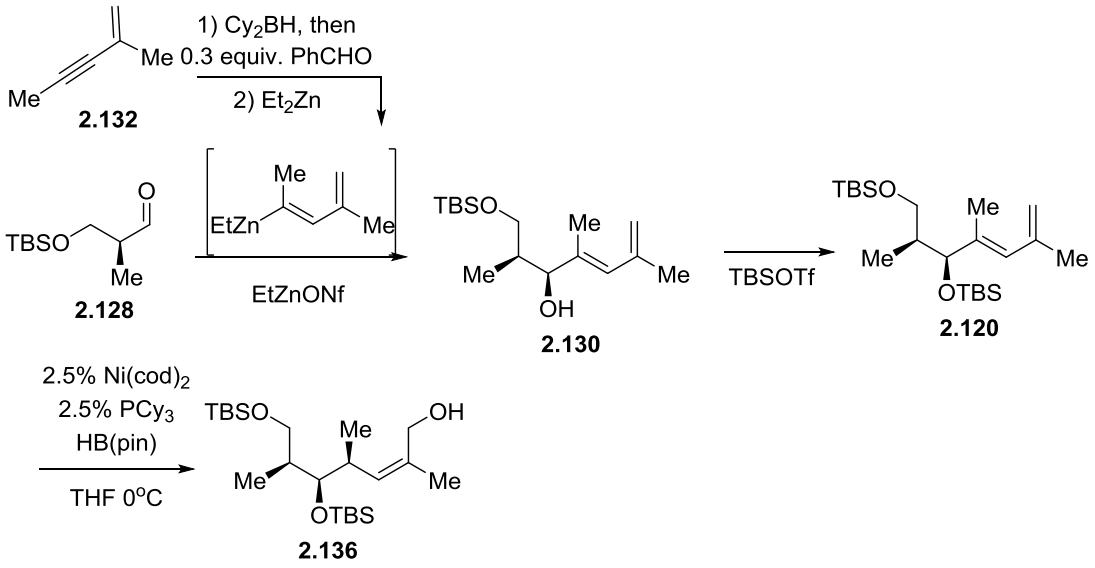
A flame-dried round-bottom flask containing a magnetic stir bar, under an atmosphere of nitrogen, was charged wtih diol **2.120-OH** (80 mg, 0.47 mmol) in CH_2Cl_2 (4 mL) and 2,6-lutidine (0.16 mL, 1.41 mmol). The reaction flask was cooled to −78 °C, followed by dropwise addition of freshly distilled TBSOTf (0.26 mL, 1.14 mmol). The

reaction was allowed to stir for 1 h or until done by TLC, then quenched with water. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (hexanes) to afford a clear, colorless oil (105.0 mg, 58%).

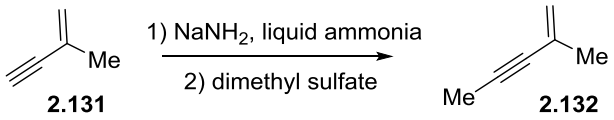


(5*S*,6*S*)-2,2,3,3,6,9,9,10,10-Nonamethyl-5-((*E*)-4-methylpenta-2,4-dien-2-yl)-4,8-dioxa-3,9-disilaundecane. (Scheme 2.18, 2.120). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72 (1H, s), 4.97 (1H, quin, *J* = 1.0 Hz), 4.79 (1H, t, *J* = 1.0 Hz), 3.76 (1H, d, *J* = 8.5 Hz), 3.73 (1H, dd, *J* = 9,5, 7.0 Hz), 3.53 (1H, dd, *J* = 9.5, 7.0 Hz), 1.84 (3H, s), 1.77-1.73 (1H, m), 1.71 (3H, s), 0.90 (9H, s), 0.88 (9H, s), 0.76 (3H, d, *J* = 6.5 Hz), 0.04 (6H, s), 0.03 (3H, s), −0.03 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.9, 138.3, 129.2, 114.7, 80.9, 65.1, 40.1, 26.2, 26.1, 23.8, 18.6, 18.4, 14.1, 12.8, −4.3, −5.0, −5.1, −5.2; IR (neat): 2956 (m), 2929 (m), 2857 (m), 1462 (w), 1251 (m), 1061 (s), 834 (s), 774 (s), 668 (w); HRMS-(ESI+) for $C_{22}H_{47}O_2Si_2$ $[M+H]^+$: calculated: 399.3115, found: 399.3121. $[\alpha]_D^{21}$ = +11.476 (*c* = 1.00, $CHCl_3$, *l* = 50 mm).

ii) Synthesis of Chiral Dienol Ether without Using Auxiliary

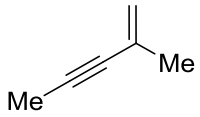


Procedure for Preparation of 1,3-Enyne 2.132



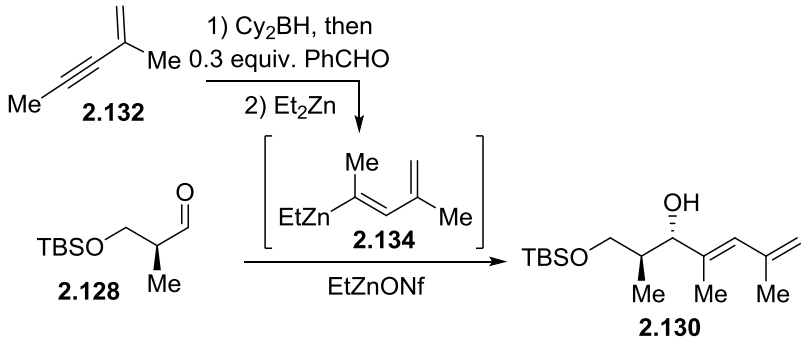
A flame dried 100 mL two-neck round bottom flask was charged with $NaNH_2$ (1.40 g, 32 mmol) and stir bar in glove box. One neck was assembled with cold finger condenser and the other neck was sealed with rubber septum. And such separate was brought out of box and connect to nitrogen line. Acetone/dry ice was added to the cold finger. Ammonia gas was introduced and condensed into the round bottom flask placed on cooling bath (isopropanol/dry ice). Ammonia gas line was removed when 15 mL liquid ammonia was collected. 2-methylbut-1-en-3-yne **2.131** (3.0 mL, 32 mmol) was added dropwise via syringe over 5 min and stirred further for 40 min. Dimethyl sulfate was added *via* cannula slowly and stirred for 1 hour at that temperature. (**NOTE:** strongly exothermic reaction! Extra caution needed). Cooling bath was removed, and the flask was allowed to warm to room temperature. Let ammonia reflux for 8 hours (keep refilling dry

ice of the cold finger). Cold finger was removed and quickly switched to rubber septum with ventilation needle leading to aqueous hydrogen chloride in Erlenmeyer flask. The ammonia was evaporated slowly by putting round bottom flask on ice bath. After all ammonia was removed, the residue was distilled under nitrogen via shortpath providing desired compound **2.132** as a colorless liquid (1.4 g, 55%) sufficiently clean and used for next step without further purification.



2-Methylpent-1-en-3-yne. **(Scheme 2.21, 2.132).** All spectrum data are in accordance with literature.[123] ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.19 (1H, s), 5.13 (1H, t, *J* = 1.5 Hz), 1.94 (3H, s), 1.86 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 127.5, 120.6, 85.1, 81.2, 24.0, 4.3.

Modified Procedure for Chelation-Controlled Additions to β-Silyloxy Aldehyde[71]

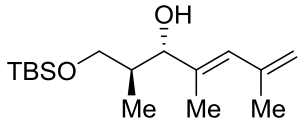


Preparation of EtZnONf: To a flame-dried 25 mL Schlenk flask equipped with magnetic stir bar and septum was added Et_2Zn (1.90 mL, 3.8 mmol, 2 M in CH_2Cl_2). The solution was cooled to –78 °C in a dry ice/acetone bath, and nonafluorobutane-1-sulfonic acid (0.56 mL, 3.8 mmol) was added dropwise. The reaction was allowed to stir at –78

[123] Baird, M. S.; Hussain, H. H.; Nethercott, W. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1845.

°C for 5 min and was allowed to warm to room temperature and stirred for 1 h resulting white slurry.

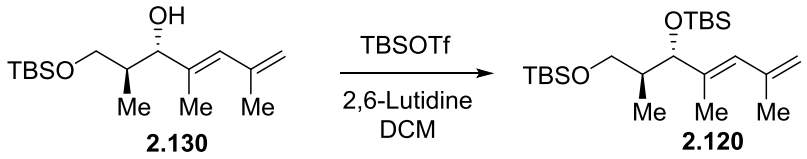
$HBCy_2$ (536 mg, 3.0 mmol) and CH_2Cl_2 (2.0 mL) was added to a flame dried 100 mL two-neck round bottom flask in glove box. The flask was cooled to 0 °C, and 2-methylpent-1-en-3-yne **2.132** (240 mg, 3.0 mmol) was added dropwise. The reaction mixture was allowed to stir at 0 °C for 5 min and then stirred at room temperature for 20 min providing a clear solution. Benzaldehyde (96 mg, 0.9 mmol) was added dropwise at room temperature and stirred for another 30 min. The flask was capped and brought out of glove box and cooled to –78 °C. Et_2Zn (1.5 mL, 2.0 M in toluene) was added dropwise and stirred at –78 °C for 30 min. EtZnONf slurry was cannula transferred to the flask at –78 °C in one portion, and the flask was transferred to a cooling bath at –20 °C. A toluene solution (8.0 mL) of the β-silyloxy aldehyde **2.128** (408 mg, 2.0 mmol) was added dropwise. The reaction was allowed to stir at –20 °C overnight. The reaction was quenched with a saturated solution of NH_4Cl (15 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The crude products were concentrated in vacuo and purified by flash chromatography on silica gel (diethyl ether:hexanes 1:10) to afford **2.130** as a colorless oil (433 mg, 76%). R_f = 0.56 (1:5 diethyl ether:hexanes, stain in $KMnO_4$).



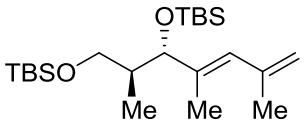
(2*S*,3*S*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,4,6-trimethylhepta-4,6-dien-3-ol (Scheme 2.22, 2.130). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.87 (1H, s), 4.99 (1H, t, *J* = 1.0 Hz), 4.07 (1H, d, *J* =2.5 Hz), 3.87 (1H, dd, *J* = 8.0, 1.0 Hz), 3.80 (1H, dd, *J* =10.0, 4.0 Hz), 3.59 (1H, dd, *J* =7.4, 9.5 Hz),

1.89 (1H, qdd, J = 7.0, 7.0, 4.0 Hz), 1.85 (3H, s), 1.79 (3H, s), 0.91 (9H, s), 0.76 (3H, d, J = 7.0 Hz), 0.09 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.9, 137.8, 129.4, 115.0, 84.4, 68.8, 37.6, 26.0, 23.9, 18.3, 13.9, 13.2, −5.4, −5.5; IR (neat): 3432 (w), 2955 (m), 2929 (m), 2857 (m), 1470 (w), 1252 (m), 1088 (s), 1005 (s), 834 (s), 775 (s); HRMS-(ESI+) for $C_{16}H_{31}OSi$ $[M-H_2O+H]^+$: calculated: 267.2144, found: 267.2138. $[\alpha]_D^{21}$ = +32.246 (c = 0.40, $CHCl_3$, l = 50 mm).

Procedure for tert-Butyldimethylsilyl Protection

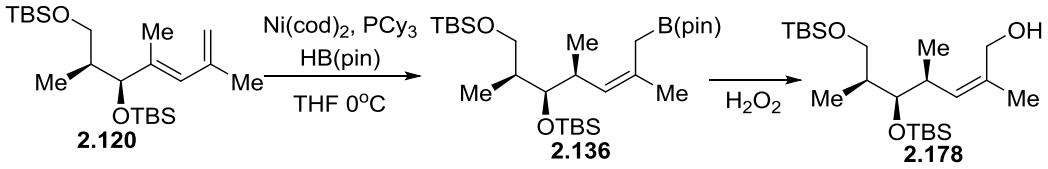


A flame-dried round-bottom flask containing a magnetic stir bar, under an atmosphere of nitrogen, was charged with alcohol **2.130** (240.0 mg, 0.84 mmol) in CH_2Cl_2 (8.4 mL) and 2,6-lutidine (0.15 mL, 1.3 mmol). The reaction flask was cooled to −78 °C, and freshly distilled TBSOTf (0.22 mL, 0.92 mmol) was added dropwise. The reaction was allowed to stir for 1 h until TLC showed full conversion of starting material, and the reaction was quenched with aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (diethyl ether:hexanes=1:20) to afford **2.120** as a clear, colorless oil (310.0 mg, 96%). R_f = 0.25 (diethyl ether:hexanes = 1:20, stain in $KMnO_4$).



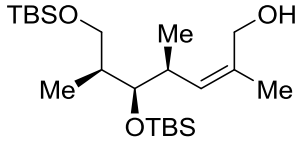
(5*S*,6*S*)-2,2,3,3,6,9,9,10,10-Nonamethyl-5-((*E*)-4-methylpenta-2,4-dien-2-yl)-4,8-dioxa-3,9-disilaundecane. (Scheme 2.22, 2.120). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72 (1H, s), 4.97 (1H, quin, *J* = 1.0 Hz), 4.79 (1H, t, *J* = 1.0 Hz), 3.76 (1H, d, *J* = 8.5 Hz), 3.73 (1H, dd, *J* = 9,5, 7.0 Hz), 3.53 (1H, dd, *J* = 9.5, 7.0 Hz), 1.84 (3H, s), 1.77-1.73 (1H, m), 1.71 (3H, s), 0.90 (9H, s), 0.88 (9H, s), 0.76 (3H, d, *J* = 6.5 Hz), 0.04 (6H, s), 0.03 (3H, s), −0.03 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.9, 138.3, 129.2, 114.7, 80.9, 65.1, 40.1, 26.2, 26.1, 23.8, 18.6, 18.4, 14.1, 12.8, −4.3, −5.0, −5.1, −5.2; IR (neat): 2956 (m), 2929 (m), 2857 (m), 1462 (w), 1251 (m), 1061 (s), 834 (s), 774 (s), 668 (w); HRMS-(ESI+) for $C_{22}H_{47}O_2Si_2$ $[M+H]^+$: calculated: 399.3115, found: 399.3121. $[\alpha]_D^{21}$ = +11.476 (*c* = 1.00, $CHCl_3$, *l* = 50 mm).

Procedure for Diastereoselective Hydroboration of 1,3-Dienol



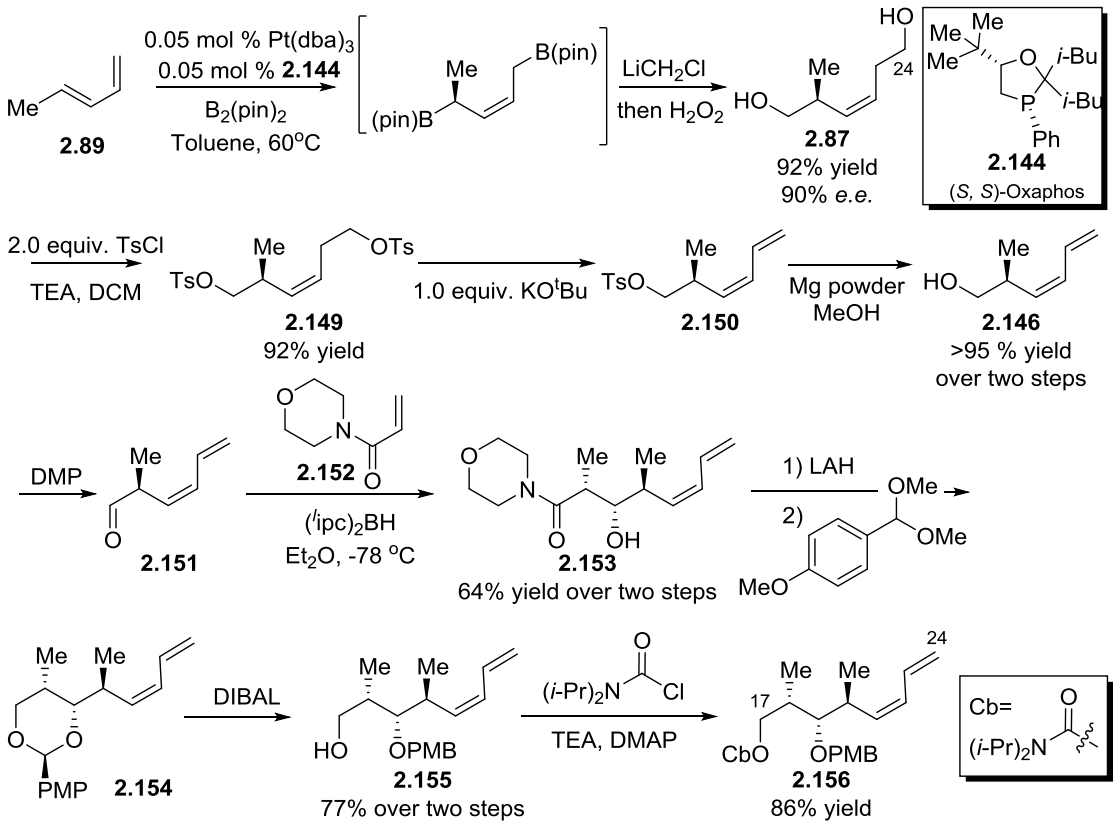
In dry-box, an oven-dried 6-dram vial containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (10.0 mg, 0.034 mmol), PCy_3 (10.0 mg, 0.034 mmol), THF (6.75 mL, 0.25M), and diene **2.120** (510 mg, 1.35 mmol). The vial was placed in the freezer in glove box for 10 min, and pinacolborane (185 mg, 1.45 mmol) was added while the vial was cold. The vial was sealed with a polypropylene cap, removed from the dry-box, immediately cooled to 0°C (ice/water), and allowed to stir overnight. The reaction mixture was kept at 0 °C and charged with 3.0 mL pH=7 buffer and 1.0 mL 30% *w/w* H_2O_2. The reaction was gradually warmed to room temperature and allowed to stir

for 12 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate was added dropwise. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (diethyl ether:hexanes = 1: 10) to afford **2.178** as a clear, colorless oil (480 mg, 92%, 9:1 dr). R_f = 0.38 (5:1 hexanes:diethyl ether, stain in $KMnO_4$).

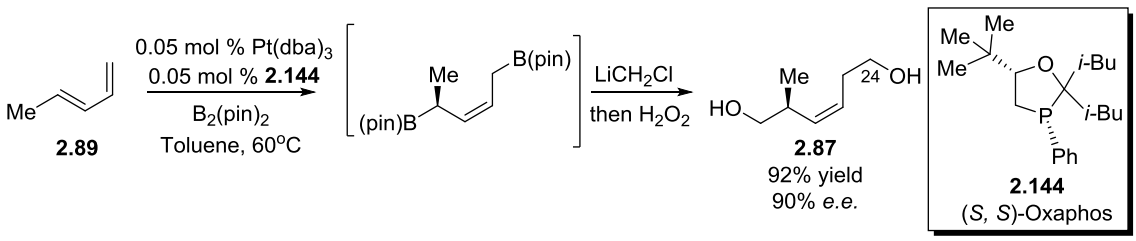


(4*S*,5*R*,6*S*,*Z*)-5,7-Bis((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethylhept-2-en-1-ol. (Scheme 2.25, boronic ester 2.136 was characterized as its alcohol 2.178) ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 (1H, d, *J* = 10.0 Hz), 4.18 (1H, dd, *J* = 10.0, 5.5 Hz), 3.99 (1H, dd, *J* = 12.0, 7.0 Hz), 3.72 (1H, dd, *J* = 10.0, 5.5 Hz), 3.41 (1H, dd, *J* = 6.0, 4.5 Hz), 3.37 (1H, dd, *J* =10.0, 7.5 Hz), 2.69 (1H, dqd, *J* = 10.0, 6.5, 6.5 Hz), 1.90-1.85 (1H, m), 1.79 (3H, s), 0.94 (3H, d, *J* = 6.5 Hz), 0.91 (3H, d, *J* = 5.5 Hz), 0.91 (9H, s), 0.90 (9H, s), 0.05 (12H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.7, 133.1, 78.7, 65.7, 62.0, 40.5, 36.0, 26.4, 26.2, 21.9, 18.7, 18.6, 17.7, 15.0, −3.6, −3.7, −5.1, −5.2; IR (neat): 3347 (w), 2955 (m), 2929 (m), 2856 (m), 1472 (w), 1251 (m), 1083 (m), 1004 (m), 833 (s), 771 (s), 668 (w); HRMS-(ESI+) for $C_{22}H_{49}O_3Si_2$ $[M+H]^+$: calculated: 417.3220, found: 417.3236. $[\alpha]_D^{21}$ = −9.486 (*c* = 0.52, $CHCl_3$, *l* = 50 mm).

III. C16-C24 fragment

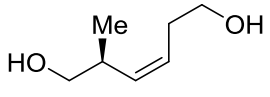


Procedure for Diboration/Homologation/Oxidation Sequence



A 100 mL flame-dried Schlenk flask vial equipped with magnetic stir bar in the dry box was charged with $Pt(dba)_3$ (7.9 mg, 8.8 μmol), followed by the addition of toluene (16.0 mL). (3*S*,5*S*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane **2.144**[44b] was added as a solution in toluene (0.0913 M, 0.19 mL, 17.3 μmol), followed by $B_2(pin)_2$ (4.7 g, 18.5 mmol). The flask was then sealed, removed from the dry box and heated to 80 °C for 20 minutes, during which the reaction mixture changes from a dark

purple solution to a light yellow solution. After cooling to room temperature, the flask was returned to the dry box and (*E*)-penta-1,3-diene **2.89** (1.20 g, 17.6 mmol) was added. The vial was sealed, removed from the dry box, and heated to 60 ^{o}C for 20 hours. Majority of the solvent was then removed by rotary evaporation and the flask was purged with N_2. The flask was then charged with THF (100 mL) and bromochloromethane (3.53 mL, 52.8 mmol) and cooled to −78 °C. *n*-BuLi (2.50 M in hexanes 21.0 mL, 52.8 mmol) was then added dropwise *via* syringe. After being allowed to stir for 10 min at −78 °C the reaction was allowed to warm to room temperature slowly and stirred for 12 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (30 mL), and 30 *w/w* % hydrogen peroxide (15 mL). The reaction was allowed to warm to room temperature and stir for 4 h, at which time the flask was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (15 mL) was added dropwise. The reaction mixture was diluted with ethyl acetate (30 mL) and water (30 mL) and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (1:2 hexanes:ethyl acetate to 100% ethylacetate) to afford the titled compound **2.87** as a clear, colorless oil (2.10 g, 92%). R_f = 0.10 (1:2 hexanes:ethyl acetate, stain in $KMnO_4$).

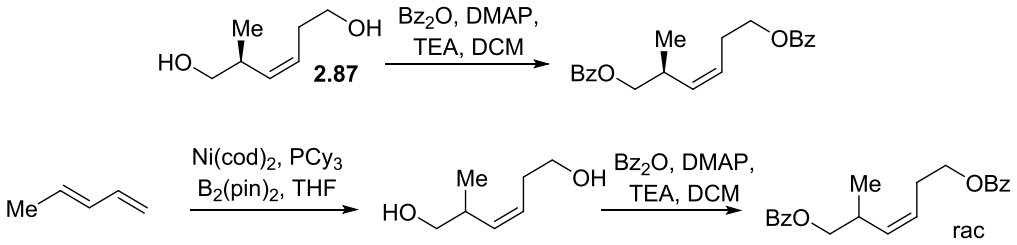


(*Z*)-2-Methylhex-3-ene-1,6-diol. (Scheme 2.26, 2.87). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.48 (1H, ddd, *J* = 10.0, 6.0, 6.0 Hz), 5.28 (1H, dd, *J* = 10.0, 10.0 Hz), 3.64 (1H, ddd, *J* = 10.0, 5.0, 5.0 Hz), 3.52 (1H, dd, *J* = 9.5, 4.0 Hz), 3.46 (1H, dd, *J* = 10.0, 5.0 Hz), 3.21 (1H, dd, 10.0, 10.0 Hz), 3.20 (2H, s, br),

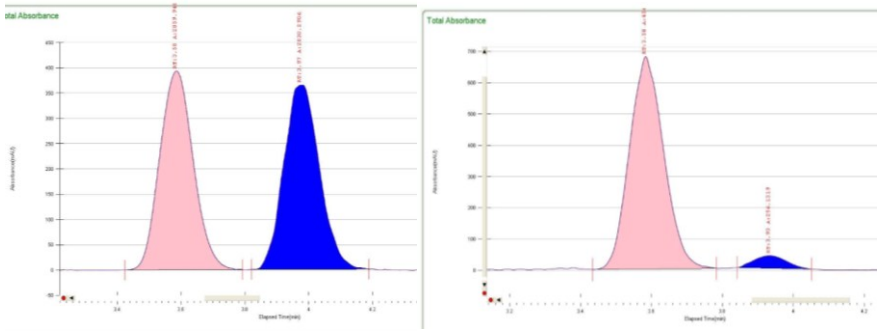
2.70-2.64 (1H, m), 2.45-2.34 (1H, m), 2.16-2.10 (1H, m), 0.84 (3H, d, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.1, 127.8, 67.7, 61.8, 34.7, 31.0, 17.2; IR (neat): 3324 (s), 3004 (s), 2956 (s), 2872 (s), 1455 (w), 1035 (s), 744 (s); HRMS-(ESI+) for $C_7H_{15}O_2$ [M+H]: calculated: 131.1078, found: 131.1072. $[\alpha]_D^{21} = -49.476$ (c = 0.64, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

The titled compound **2.87** was converted to corresponding *bis*-benzoate as shown below. The resulting *bis*-benzoate was compared to racemic material[124] prepared as shown below.



Chiral SFC (Chiralpak, AD-H, 35 °C, 5 mL/min, 10% Isopropanol, 100 bar, 210-270 nm) – analysis of bis-benzoate.

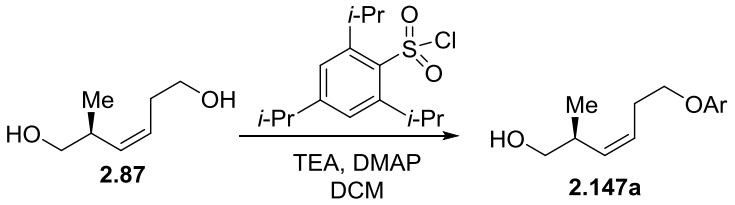


Peak Info			
Peak No	% Area	Area	RT (min)
1	50.2606	2859.9489	3.58
2	49.7394	2830.2906	3.97
Total:	100	5690.2395	

Peak Info			
Peak No	% Area	Area	RT (min)
1	94.6819	4560.0538	3.58
2	5.3181	256.1319	3.93
Total:	100	4816.1857	

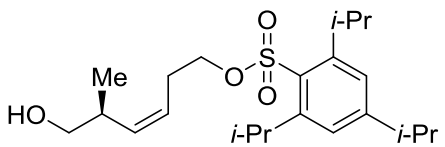
[124] Ely, R. J.; Morken, J. P. *Org. Lett.* **2010,** *12*, 4348.

Procedure for Monosulfonylation of 1,6-Diol via Flow Chemistry



2.87 2.147a

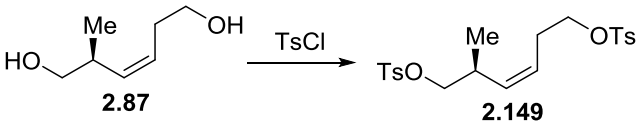
All tubing and connectors were purchased from Upchurch Science and assembled as described in literature (Scheme 2.26d).[85] Then the tubing was flushed with dry 5 mL CH_2Cl_2. One syringe was charged with a dry 1.0 mL CH_2Cl_2 solution of diol **2.87** (50 mg, 0.385 mmol) while the second syringe with a dry CH_2Cl_2 solution of TEA (83 μL, 0.587 mmol), DMAP (9.4 mg, 0.077 mmol) and sulfonyl chloride (127 mg, 0.385 mmol). The two syringes were pushed together by a syringe pump at a rate of 0.25 mL/min, and the two solutions were mixed together in ice bath *via* a T-connector (calculated reaction time to be 4.24h at 0°C). The end of flow reactor was connected to a vial containing water to quench reaction. The two layer mixture was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The bis-sulfonylation to mono-sulfonylation ratio was 2:1 as determined by ^{1}H NMR and the regioselectivity was 4:1. The crude material was purified on silica gel chromatography to afford titled compound as a mixture of regioisomers.



(*S*,*Z*)-6-Hydroxy-5-methylhex-3-en-1-yl-2,4,6-triisopropylbenzenesulfonate (Scheme 2.27, 2.147a). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (2H, s), 5.48-5.43 (1H, m), 5.33-5.29 (1H, m), 4.07-4.03 (2H, m), 3.48 (1H, dd, *J* = 10.5, 6.0 Hz), 3.33 (1H, dd, *J* = 10.5, 8.0 Hz), [minor regioisomer 3.87 (1H, dd, *J* = 6.5, 3.0 Hz), 3.62 (1H, dd, *J* = 7.0, 7.0 Hz)], 2.93

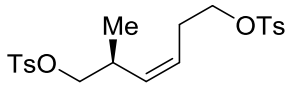
(1H, m), 2.65 (1H, m), 2.50 (2H, q, J = 7.0 Hz), 1.25 (18H, d, J = 7.0 Hz), 0.92 (3H, d, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.9, 151.0, 136.3, 127.8, 125.4, 123.9, 68.9, 67.7, 35.2, 34.4, 29.8, 27.8, 24.9, 23.7, 17.0; IR (neat): 3392 (w), 2957 (s), 2930 (m), 2871 (w), 1600 (w), 1462 (w), 1374 (m), 1177 (s), 1040 (m), 962 (m), 905 (m), 806 (w), 779 (m), 750 (m), 563 (m). $[\alpha]_D^{21}$ = +4.696 (c = 0.7, $CHCl_3$, l = 50 mm).

Procedure for bis-Tosylation of 1,6-Diol



2.87 **2.149**

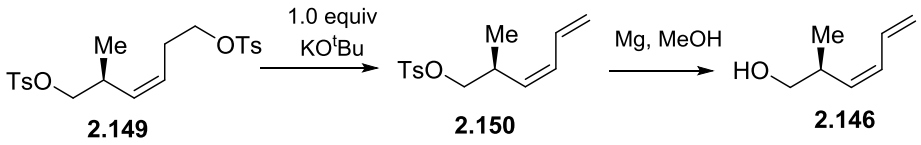
To a flame-dried 100 mL round-bottom flask equipped with a magnetic stir bar was added diol **2.87** (2.1 g, 16.9 mmol) in CH_2Cl_2 (30 mL) and NEt_3 (8.0 mL, 55.8 mmol) as well as DMAP (103 mg, 0.85 mmol). The flask was cooled to 0 °C and a CH_2Cl_2 solution (26 mL) of *p*-toluenesulfonyl chloride (7.1 g, 37.2 mmol) was added. The reaction was allowed to warm to room temperature and stir for 12 h. The crude slurry was then filtered through a plug of silica gel, rinsing with CH_2Cl_2, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (4:1 hexanes:ethyl acetate) to afford **2.149** as a clear, light yellow oil (7.0 g, 94%). R_f = 0.30 (4:1 hexanes:ethyl acetate, stain in $KMnO_4$).



(*Z*)-2-Methylhex-3-ene-1,6-diyl-bis(4-methylbenzenesulfonate) (Scheme 2.28, 2.149). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79-7.75 (4H, m), 7.34-7.33 (4H, m), 5.30 (1H, ddt, J = 11.0, 7.5, 1.0 Hz), 5.17 (1H, ddd, J = 11.0, 11.0, 1.5 Hz), 4.03 (2H, m), 3.81-3.75 (2H, m), 2.72 (1H,

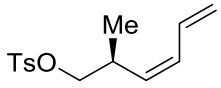
qdtd, J = 11.0, 7.0, 5.0, 1.0 Hz), 2.45 (6H, s), 2.35 (2H, dt, J = 7.5 Hz), 0.91 (3H, d, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.0, 133.8, 133.3, 130.1, 128.1, 125.6, 74.0, 69.6, 32.1, 27.6, 21.9, 17.1; IR (neat): 2964 (w), 2927 (w), 1598 (w), 1357 (m), 1175 (s), 964 (m), 815 (m), 665 (m), 554 (m); HRMS-(ESI+) for $C_{21}H_{27}O_6S_2$ $[M+H]^+$: calculated: 439.1236, found: 439.1249. $[\alpha]_D^{21}$ = +27.642 (c = 0.68, $CHCl_3$, l = 50 mm).

Procedure for Selective Elimination and Tosylate Removal



2.149 **2.150** **2.146**

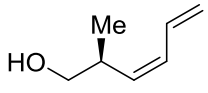
To a flame-dried 50 mL round-bottom flask equipped with a magnetic stir bar was added bistosylate **2.149** (6.0 g, 13.7 mmol) in dry THF (130 mL) under nitrogen. The reaction was cooled to 0 °C and KO*t*Bu (1.50 g, 13.7 mmol) was added dropwise as a solution in THF (7 mL). The reaction was allowed to warm to room temperature and stirred for 30 min then concentrated by rotary evaporation. The crude oil was filtered through a short plug of silica gel, washing with Et_2O, and concentrated to afford **2.150** as a clear, colorless oil. The material was used for next step without further purification.



(*Z*)-2-Methylhexa-3,5-dien-1-yl-4-methylbenzenesulfonate (Scheme 2.28, 2.150). Occasionally the titled compound **2.150** was purified for characterization. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (2H, m), 7.34 (2H, m), 6.48 (1H, dddd, J = 17.0 Hz, 12.0 Hz, 12.0 Hz, 1.0 Hz), 5.99 (1H, ddd, J = 12.0 Hz, 12.0 Hz, 0.5 Hz), 5.21 (1H, ddd, J = 17.0 Hz, 1.0 Hz, 0.5 Hz), 5.14 (1H, ddd, J = 12.0 Hz, 1.0 Hz, 0.5 Hz), 5.10 (1H, dd, 11.5 Hz, 11.5 Hz), 3.89-3.81 (2H, m), 2.99 (1H, m), 2.45 (3H,

s), 1.00 (3H, 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 133.9, 131.9, 131.2, 130.0, 128.1, 128.1, 119.1, 74.1, 32.4, 21.8, 17.4; IR (neat): 3073 (w), 2957 (s), 2871 (m), 1731 (s), 1359 (m), 1267 (m), 1086 (s), 990 (m); HRMS-(ESI+) for $C_{14}H_{22}NO_3S$ $[M+NH_4]^+$: calculated: 284.1320, found: 284.1326. $[\alpha]_D^{21} = +71.840$ (*c* = 0.64, $CHCl_3$, *l* = 50 mm).

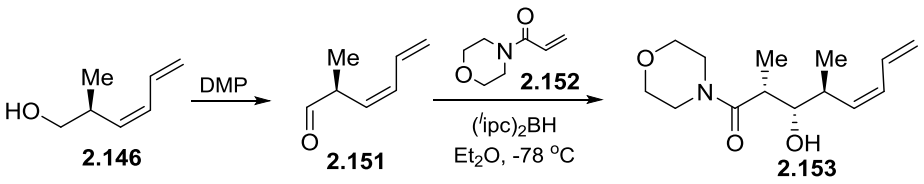
The procedure for tosylate removal was reported in literature.[125] Mg powder (383 mg, 16.0 mmol) was added to a flame dried 100 mL round bottom flask equipped with magnetic stir bar in glove box, which was capped and removed from box. The flask was cooled on an ice bath and then charged with freshly distill MeOH (10 mL). A MeOH (6 mL) solution of tosylate **2.150** (850 mg, 3.2 mmol) was added dropwise. The reaction was allowed to warm to room temperature slowly and stirred overnight (though reaction usually completes in 3 hours). Reaction was quenched by slow addition of 1.0 M HCl aqueous solution on ice bath and then diluted with ethylacetate. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (diethyl ether:hexanes=1:2) to afford the titled compound as a clear, colorless oil (360 mg, >95% over two steps). R_f = 0.56 (1:2 hexanes:ethyl acetate, stain in $KMnO_4$).



(*S*,*Z*)-2-Methylhexa-3,5-dien-1-ol. **(Scheme 2.28, 2.146)** All spectrum data are in accordance with literature.[126]

[125] Sridhar, M.; Kumar, B. A.; Narender, R. *Tetrahedron Lett.* **1998**, *39*, 2847.
[126] Francavilla, C.; Chen, W. C.; Kinder, F. R. *Org. Lett.* **2003**. *5*, 1233**.**

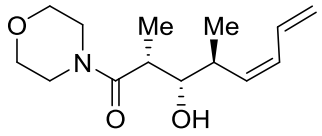
Slightly Modified Procedure for the Reductive Aldol Reaction[87]



A flame dried 100 mL round bottom flask was charged with Dess-Martin periodinae (976 mg, 2.3 mmol) and $NaHCO_3$ (2.0 g, 23 mmol), and the flask was purged with nitrogen. A CH_2Cl_2 solution of alcohol **2.146** (220 mg, 2.0 mmol) was added in one portion at room temperature and the reaction mixture was stirred for 2 hours to reach completion. Reaction was quenched with saturated $Na_2S_2O_3$ solution and stirred for 10 min at room temperature. Layers were separated and aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation carefully. Light yellow residue was passed through a plug of silica gel with Et_2O and concentrated by rotary evaporation carefully to give desired aldehyde **2.151** as clear slight yellow oil, which was used for next step without further purification. All spectrum data are in accordance with literature.[126]

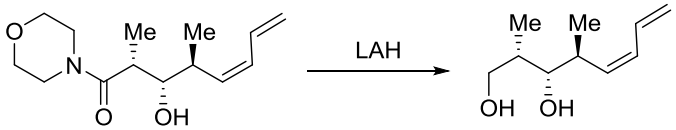
To a suspension of (^{l}Ipc)$_2$BH (weighed in the glove box, 640 mg, 2.4 mmol) in Et_2O (10 mL) at 0 °C was added 4-acryloylmorpholine **2.152** (326 μL, 2.6 mmol). The solution was stirred for 2 h at 0 °C resulted a clear solution. The resulting mixture was cooled to −78 °C, aldehyde **2.151** (max = 2.0 mmol) in ether (1.0 mL) was added dropwise, and the solution was stirred overnight at −78 °C. Reaction flask was charged with 2-methylaminoethanol (0.3 mL) and MeCN (10 mL) and temperature was increased to 80 ^{o}C and stirred for 6 hours. After cooling back to room temperature, the mixture was concentrated under reduced pressure. The residue was purified by flash chromatography

(1:1 hexanes:ethyl acetate to ethyl acetate) provided the β–hydroxymorpholine amide **2.153** as white solid (310 mg, 62% over two steps). R_f = 0.54 (ethyl acetate, stain in $KMnO_4$).



(2*R*,3*S*,4*S*,*Z*)-3-Hydroxy-2,4-dimethyl-1-morpholinoocta-5,7-dien-1-one (Scheme 2.28, 2.153). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.55 (1H, dt, *J* = 17.5, 10.0 Hz), 6.07 (1H, t, 10.5 Hz), 5.49 (1H, t, *J* = 10.5 Hz), 5.22 (1H, dt, *J* = 16.5, 1.0 Hz), 5.11 (1H, d, *J* = 9.5 Hz), 3.78 (1H, t, *J* = 5.5 Hz), 3.76-3.68 (3H, m), 3.63-3.57 (2H, m), 3.48-3.38 (3H, m), 2.85 (1H, dqd, *J* = 10.0, 6.0, 6.0 Hz), 2.69 (1H, qd, *J* = 7.0, 7.0 Hz), 1.20 (3H, d, *J* = 7.0 Hz), 1.02 (3H, d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 134.3. 132.5, 130.0, 118.1, 76.4, 67.0, 66.8, 46.2, 42.0, 38.3, 35.2, 18.2, 12.9; IR (neat): 3419 (m), 2965 (m), 2928 (m), 2867 (m), 1618 (s), 1462 (m), 1437 (m), 1224 (m), 1115 (s), 1026 (m), 989 (m), 585 (w); HRMS-(ESI+) for $C_{14}H_{24}NO_3$ $[M+H]^+$: calculated: 254.1756, found: 254.1759. $[\alpha]_D^{21}$ = +45.654 (*c* = 0.20, $CHCl_3$, *l* = 50 mm).

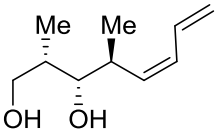
Procedure for Reduction of Morpholine Amide to Alcohol



2.153 **2.154-OH**

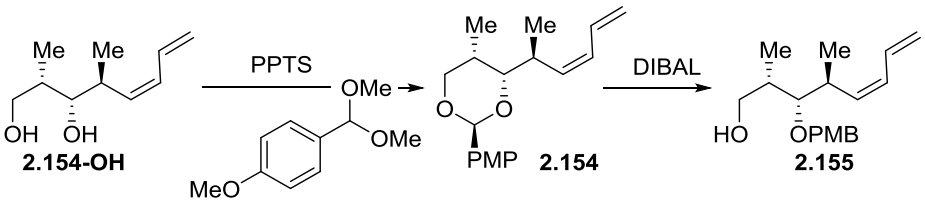
To a solution of aldol adduct **2.153** (300 mg, 1.2 mmol) in THF (12 mL) was slowly added at −78 °C under inert atmosphere a solution of lithium aluminum hydride (1 M in Et_2O, 12 mL, 1.2 mmol); the reaction mixture was stirred at this temperature for 12 h. A saturated aqueous solution of NH_4Cl (3 mL) was then added followed by CH_2Cl_2 (10

mL) and the mixture was allowed to warm up to room temperature. The aqueous layer was extracted two times with CH_2Cl_2 (10 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduce pressure. The crude aldehyde was dissolved in THF (12 mL) and the solution was cooled to -78 °C. A solution of lithium aluminum hydride (1M in Et_2O, 12 mL, 12 mmol) was added dropwise under inert atmosphere and the reaction mixture was allowed to stir for 15 minutes. At that time, a saturated aqueous solution of Rochelle's salt (3 mL) was added followed by CH_2Cl_2 (10 mL) and the mixture was stir at room temperature until complete separation of layers. The aqueous layer was extracted two times with CH_2Cl_2 (10 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduce pressure. Crude material was purified on silica gel chromatography to afford titled compound **2.154-OH** as colorless oil (115 mg, 80%). R_f = 0.33 (EtOAc : hexane = 1:1).



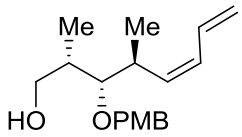
(2*S*,3*S*,4*S*,*Z*)-2,4-Dimethylocta-5,7-diene-1,3-diol (Scheme 2.28, 2.154-OH) ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.63 (1H, dt, *J* = 17.0, 11.0 Hz), 6.17 (1H, t, *J* = 11.0 Hz), 5.29 (1H, t, *J* = 10.5 Hz), 5.25 (1H, d, *J* = 17.0), 5.16 (1H, d, *J* = 10.5 Hz), 3.74 (1H, ddd, *J* = 10.5, 4.0, 2.0 Hz), 3.68 (1H, ddd, *J* = 10.5, 6.0, 1.5 Hz), 3.51 (1H, dd, *J* = 9.0, 2.0 Hz), 2.79 (1H, qdd, *J* = 7.5, 7.5, 7.5 Hz), 2.23 (2H, bs), 1.89-1.85 (1H, m), 1.00 (3H, dd, *J* = 7.0, 1.5 Hz), 0.95 (3H, dd, *J* = 7.0, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.8, 132.2, 131.8, 119.0, 67.8, 36.5, 36.0, 17.0, 9.1; IR (neat): 3355 (b), 2965 (s), 2931 (s), 2876 (m), 1457 (m), 1434 (w), 1378 (w), 1026 (s), 981 (s), 903 (s), 794 (w), 664 (m); HRMS-(ESI+) for $C_{10}H_{19}O_2$ $[M+H]^+$: calculated: 171.1385, found: 171.1386. $[\alpha]_D^{21} = -5.263$ (*c* = 0.30, $CHCl_3$, *l* = 50 mm).

Procedure for Acetal Protection and Selective Acetal Opening



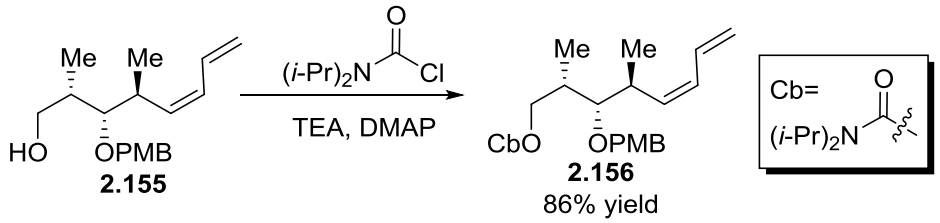
Diol **2.154-OH** (115 mg, 0.68 mmol) and dimethoxyl acetal (185 mg, 1.01 mmol) was dissolved in 2 mL dry CH_2Cl_2 and catalytic amount of PPTS was added at room temperature. Water was added to quench reaction when TLC indicated full conversion of starting material. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduce pressure. Crude material **2.154** was used for next step without further purification.

Crude **2.154** was dissolved in 20 mL dry CH_2Cl_2 under N_2 and cool to 0 ^oC. DIBAL (0.36 mL, 2.04 mmol) was added dropwise and the mixture was allowed to stir at 0 ^oC until TLC showed full conversion of starting material (usually in two hours). Reaction was carefully quenched with a saturated aqueous solution of Rochelle's salt (15 mL) was added followed by CH_2Cl_2 (3 mL) and the mixture was stir at room temperature until complete separation of layer. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL), the combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduce pressure. Crude material was purified on silica gel chromatography to afford titled compound **2.155** as colorless oil (152 mg, 77% over two steps). R_f = 0.24 (EtOAc : hexane = 1:4).

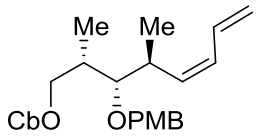


(2*S*,3*S*,4*S*,*Z*)-3-((4-Methoxybenzyl)oxy)-2,4-dimethylocta-5,7-dien-1-ol (Scheme 2.28, 2.155). All spectrum data are in accordance with literature.[37b]

Procedure for the Synthesis of Carbamate



To a solution of *N,N*-diisopropylcarbamoyl chloride (81 mg, 0.42 mmol) and NEt_3 (90 μL, 0.51 mmol) in CH_2Cl_2 (1.0 mL) was added alcohol **2.155** (120 mg, 0.42 mmol). This mixture was then heated to reflux and stirred for 24h. The reaction was cooled to rt and H_2O (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduce pressure. Crude material was purified on silica gel chromatography to afford titled compound **2.156** as colorless oil (150 mg, 86% yield). R_f = 0.18 (EtOAc : hexane = 1:4).



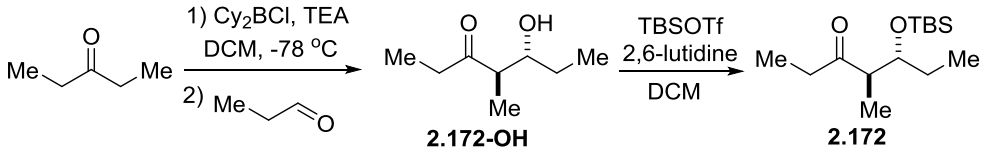
(2*S*,3*S*,4*S*,*Z*)-3-((4-Methoxybenzyl)oxy)-2,4-dimethylocta-5,7-dien-1-yl diisopropylcarbamate (Scheme 2.28, 2.156). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (2H, d, *J* = 8.5 Hz), 6.87 (3H, d, *J* = 9.0 Hz), 6.67 (1H, dt, *J* = 17.0, 11.0 Hz), 6.05 (1H, t, *J* = 11.0 Hz), 5.51 (1H, t, *J* = 10.0 Hz), 5.22 (1H, d, *J* = 17.0 Hz), 5.12 (1H, d, *J* = 10.0 Hz), 4.57 (1H, d, *J* = 10.5 Hz), 4.45 (1H, d, *J* =10.5 Hz), 4.09 (1H, dd, *J* = 11.0, 6.5 Hz), 4.04 (1H, dd, *J* = 10.5, 6.5 Hz), 3.81 (3H, s), 3.35 (1H, dd, *J* = 6.0, 4.0 Hz), 3.00 (1H, dqd, *J* = 10.5, 6.5 Hz), 2.13-2.08 (1H, m), 1.25 (12H, d, *J* = 6.5

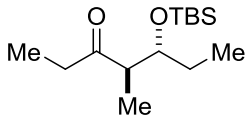
Hz), 1.04 (3H, d, J = 7.0 Hz), 1.03 (3H, d, J = 7.0Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 155.9, 135.5, 132.8, 131.2, 129..9, 129.6, 129.5, 117.6, 114.0, 113.8, 83.3, 74.6, 67.7, 55.4, 36.1, 35.7, 18.5, 12.2; IR (neat): 2963 (b), 2932 (w), 1687 (s), 1612 (w), 1514 (m), 1435 (m), 1368 (m), 1291 (s), 1247 (s), 1157 (m), 1049 (s), 823 (m), 772 (m); HRMS-(ESI+) for $C_{25}H_{40}NO_4$ $[M+H]^+$: calculated: 418.2957, found: 418.2951. $[\alpha]_D^{21}$ = +99.483 (c = 0.396, $CHCl_3$, l = 50 mm).

IV. Diastereoselective Alkylation of (E)-Enolates

i) Procedure for Ethyl Ketone Preparation

Following general *anti*-aldol procedure[127] and general TBS protection procedure, ethyl ketone **2.172** was obtained as single diastereomer.

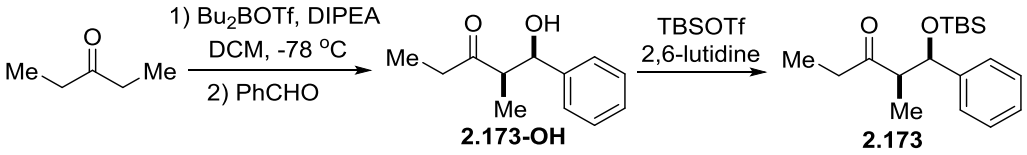


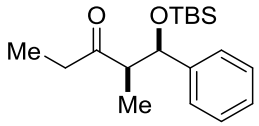


***anti*-5-((*tert*-Butyldimethylsilyl)oxy)-4-methylheptan-3-one. (Table 2.2, 2.172).** All spectrum data are in accordance with literature.[128]

[127] Brown, H. C.; Dhar, R. K. Bakshi, R. K. Pandiarajan, P. K.; Singaram, B. *J. Am. Chem. Soc.* **1989**, *111*, 3441.
[128] Arimoto, H.; Yokoyama, R; Nakamurat, K.; Okumura, Y.; Uemura, D. *Tetrahedron* **1996**. *52*, 13901.

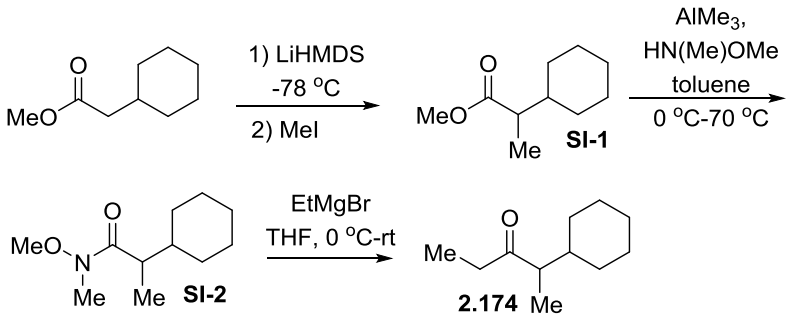
Following general *syn*-aldol procedure[129] and general TBS protection procedure, ethyl ketone **2.173** was obtained as single diastereomer.





***syn*-1-((*tert*-Butyldimethylsilyl)oxy)-2-methyl-1-phenylpentan-3-one (Table 2.2**, **2.173).** And all spectrum data are in accordance with literature.[130]

Ethyl ketone **2.174** was prepared as shown below.



Methylcyclohexyl acetate (600 mg, 3.8 mmol) was added to a 100 mL flame dried round bottom flask with THF (10 mL) and cooled to −78 °C. A solution of LiHMDS (1.0 M in THF/ethylbenzene, 4.4 mL, 4.4 mmol) was added to the mixture slowly and stirred for 1 h. MeI (280 µL, 4.6 mmol) was added dropwise at −78 °C and the reaction flask was allowed to warm to room temperature slowly and stirred overnight. The reaction was

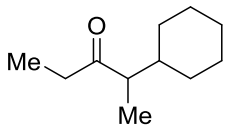
[129] Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc*. **1979**, *101*, 6120.
[130] Tanino, K.; Aoyagi, K.; Kirihara, Y.; Ito, Y.; Miyashita, M. *Tetrahedron Lett.* **2005**, *26*, 1169.

quenched with NH_4Cl aqueous solution and diluted with ethylacetate. The layers were separated and aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography to afford **SI-1** as clear colorless oil (540 mg, 83%). R_f =0.55 (ethyl acetae:hexanes=1:10, stain in $KMnO_4$)

$AlMe_3$ (1.0 M in CH_2Cl_2, 9.5 mL, 9.5 mmol) was added to a toluene (10.0 mL) suspension of HN(OMe)Me·HCl (910 mg, 9.53 mmol) at 0 ^oC dropwise and stirred for another 30 min. A toluene (3.0 mL) solution of methyl ester **SI-1** (540 mg, 3.18 mmol) was added dropwise and stirred for 2 h at 0 ^oC. The reaction was heated to 70 ^oC and stirred overnight. After cooled back to room temperature, the reaction was quenched with NH_4Cl aqueous solution and diluted with ethylacetate. The layers were separated and aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography to afford the Weinreb amide **SI-2** as a clear colorless oil (310 mg, 50%). R_f =0.49 (ethyl acetae:hexanes=1:3, stain in $KMnO_4$)

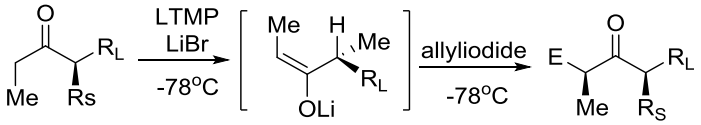
The Weinreb amide **SI-2** (310 mg, 0.8 mmol) was dissolved in dry THF (6.0 mL) in a round bottom flask equipped with magnetic stir bar. Ethyl magnesium bromide (3.0 M in Et_2O, 1.6 mL, 1.6 mmol) was added dropwise at 0 ^oC. The reaction was allowed to warm to room temperature slowly and stirred overnight. The reaction was quenched by slow addition of 1.0 M HCl aqueous solution on ice bath. The layers were separated and

the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel to afford the titled compound **2.174** as a clear, colorless oil (160 mg, 61%). R_f = 0.65 (ethyl acetate: hexanes=1:10, stain in $KMnO_4$)



2-Cyclohexylpentan-3-one. **(Table 2.2, 2.174)**. All spectrum data are in accordance with literature.[131]

ii) General Procedure for (E)-Enolate Alkylation

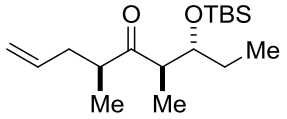


2.169 **2.170** **2.171**

The (*E*)-enolates were prepared following literature procedure.[99] To a rapidly stirred suspension of TMP·HBr (1.0 equiv.) and a spatula-tip of 1,10-phenanthroline in THF at 0 °C under nitrogen was added a 2.50 M solution of *n*-BuLi in hexanes dropwise until deep red color persisted and disappearance of any solid. Then a second portion of the same volume of *n*-BuLi was added to the dark red solution. After being stirred for an additional 3 min at 0 °C, the resulted dark red solution was cooled to −78 °C and corresponding ethyl ketone (1.0 equiv.) was added as a 10% solution in THF dropwise. Such solution was stirred at −78 °C for 30 min followed by addition of allyl iodide (1.5 equiv.) dropwise at −78 °C and stirred overnight until TLC showed full conversion of ethyl ketone. The reaction was quenched with aqueous NH_4Cl and allowed to warm to

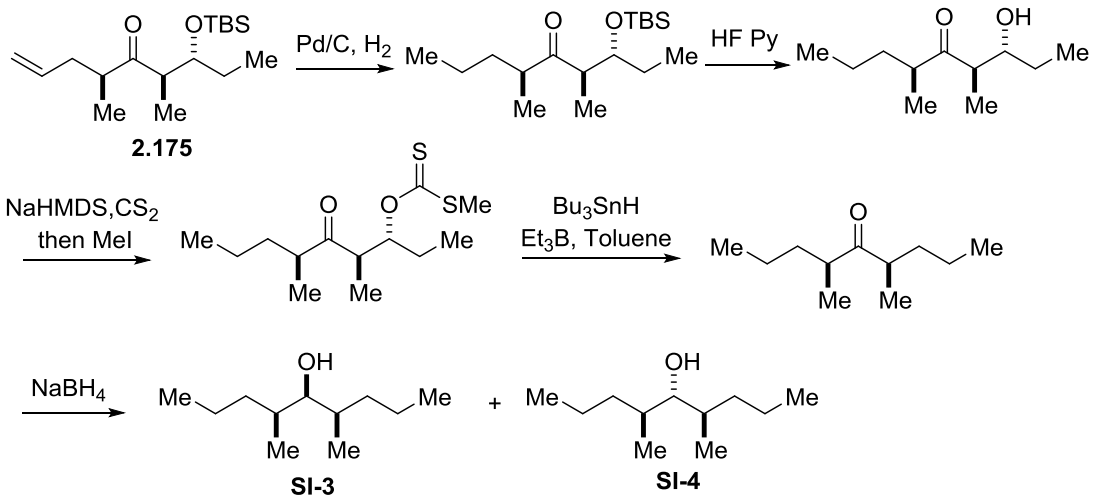
[131] Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, *12,* 1283.

room temperature. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Diastereoselectivity (d.r.) was determined by ^{1}H NMR. The crude reaction mixture was purified by silica gel chromatography.

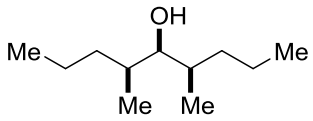


(4*S*,6*R*,7*R*)/(4*R*,6*S*,7*S*)-7-((*tert*-Butyldimethylsilyl)oxy)-4,6-dimethylnon-1-en-5-one. (Table 4.2, 2.175). The titled compound **2.175** was prepared according to enolate alkylation general procedure with ethyl ketone **2.172** (40.0 mg, 0.15 mmol), TMP·HBr (33.3 mg, 0.15 mmol), allyl iodide (23 μL, 0.23 mmol) and THF (3.8 mL) and isolated as a light yellow oil (38 mg, 85% yield, 6:1 d.r., two diastereomers are inseparable). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72 (1H, ddt, *J* = 15.5, 10.5, 6.5 Hz), 5.40 (1H, d, *J* = 15.5 Hz), 5.01 (1H, d, *J* = 10.5 Hz), 3.92 (2H, dt, *J* = 8.0, 7.5 Hz), 2.90 (1H, qd, *J* = 7.0, 7.0 Hz), 2.61 (1H, m), 2.44 (1H, dt, *J* = 14.0, 5.0 Hz), 1.47 (2H, m), 1.08 (3H, d, *J* = 7.5 Hz), 0.96 (3H, d, *J* = 6.0 Hz), 0.88 (3H, t, *J* = 7.0 Hz), 0.86 (9H, s), 0.04 (3H, s), −0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.4, 136.5, 116.8, 74.2, 49.0, 46.5, 36.5, 26.1, 25.9, 18.2, 15.9, 12.8, 7.9, −4.4, −4.5; IR (neat): 2960 (m), 2931 (m), 2882 (w), 2857 (m), 1713 (m), 1460 (m), 1369 (w), 1252 (m), 1022 (s), 996 (s), 865 (m), 833 (s), 774 (s); HRMS-(ESI+) for $C_{17}H_{35}O_2Si$ $[M+H]^+$: calculated: 299.2406, found: 299.2412.

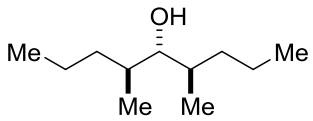
Proof of Stereochemistry



The titled compound **2.175** was converted to the corresponding alcohols **SI-3** and **SI-4** which were separable by silica gel chromatography. The spectrum data of **SI-3**[132] and **SI-4**[133] were compared with literature and completely matched.



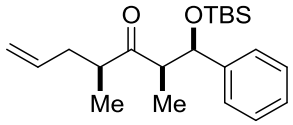
(4*R*,5*r*,6*S*)/(4*S*,5*s*,6*R*)-4,6-Dimethylnonan-5-ol (SI-3). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.19 (1H, dd, *J* = 5.5, 5.5 Hz), 1.65-1.60 (2H, m), 1.40-1.25 (6H, m), 1.17-1.11 (2H, m), 0.90 (6H, t, *J* = 7.0 Hz), 0.89 (6H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.9, 36.2, 35.2, 20.3, 14.6, 14.4. R_f = 0.40 (ethylacetate:hexanes=1:10, stain in $KMnO_4$).



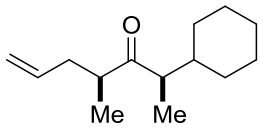
(4*R*,5*s*,6*S*)/(4*S*,5*r*,6*R*)-4,6-Dimethylnonan-5-ol (SI-4). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.10 (1H, dd, *J* = 6.0, 6.0 Hz),

[132] Brady, P. B.; Yamamoto, H. *Angew. Chem. Int. Ed*. **2012**, *51*, 1942.
[133] Whitesell, J. K.; Hildebrandt, B. *J. Org. Chem*. **1985**, *50*, 4975.

1.65-1.60 (2H, m), 1.55-1.42 (4H, m), 1.26-1.19 (4H, m), 0.91 (6H, t, J = 7.0 Hz), 0.89 (6H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 81.3, 35.4, 33.2, 20.5, 16.8, 14.7. R_f = 0.47 (ethylacetate:hexanes=1:10, stain in $KMnO_4$).

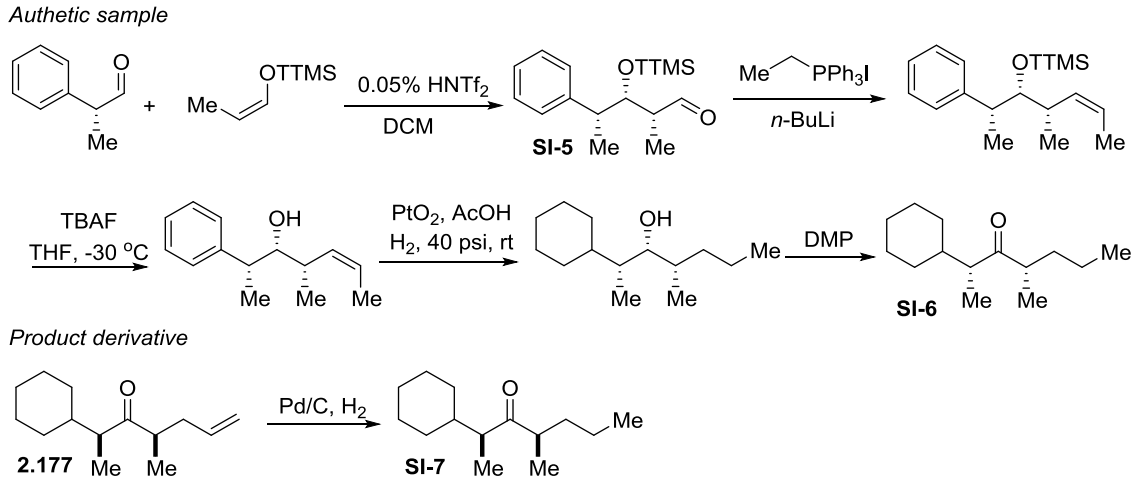


(1*R*,2*R*,4*S*)/(1*S*,2*S*,4*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,4-dimethyl-1-phenylhept-6-en-3-one. (Table 2.2, 2.176). The titled compound **2.176** was prepared according to enolate alkylation general procedure with ethyl ketone **2.173** (30.6 mg, 0.1 mmol), TMP·HBr (22.2 mg, 0.1 mmol), allyl iodide (15 μL, 0.15 mmol) and THF (1.9 mL) and was isolated as a light yellow oil (32 mg, 92% yield, 7:1 d.r., two diastereomers are inseparable). Stereochemistry was assigned by analogy. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.20 (5H, m), 5.26 (1H, dtd, J = 8.5, 8.5, 6.5 Hz), 4.83 (1H, d. J = 11.0 Hz), 4.79 (1H, d, J = 17.0 Hz), 4.67 (1H, d, J = 9.0 Hz), 3.04 (1H, dq, J = 7.0, 7.0 Hz), 2.02 (1H, qt, J = 6.5, 2.0 Hz), 1.86 (1H, ddd, J = 16.0, 6.5, 6.5 Hz), 1.63 (1H, ddd, J = 13.0, 8.0, 8.0 Hz), 1.25 (3H, d, J = 6.5 Hz), 0.90 (3H, d, J = 7.5 Hz), 0.87 (9H, s), 0.05 (3H, s), −0.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 216.2, 143.9, 136.0, 128.3, 127.7, 127.1, 116.5, 77.0, 54.9, 46.8, 35.4, 26.0, 18.4, 15.4, 15.3, −4.3, −4.8; IR (neat): 2958 (s), 2931 (s), 2887 (w), 2858 (m), 1710 (s), 1455 (w), 1362 (w), 1256 (m), 10087 (s), 1067 (s), 999 (s), 914 (w), 872 (s), 837 (s), 777 (s), 701 (s); HRMS-(ESI+) for $C_{21}H_{35}O_2Si$ $[M+H]^+$: calculated: 347.2406, found: 347.2415.

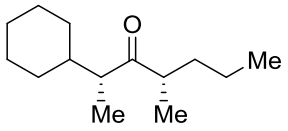


(2*R*,4*S*)/(2*S*,4*R*)-2-Cyclohexyl-4-methylhept-6-en-3-one. (Table 2.2, 2.177). The titled compound **2.177** was prepared according to enolate alkylation general procedure with ethyl ketone **2.174** (14.0 mg, 0.085 mmol), TMP·HBr (19.0 mg, 0.085 mmol), allyl iodide (12 μL, 0.13 mmol) and THF (1.9 mL). Product was obtained as light yellow oil (13 mg, 74% yield, 3:1 d.r., two diastereomers are inseparable). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72 (1H, ddt, *J* = 17.5, 11.5, 7.5 Hz), 5.44 (1H, d, *J* = 17.5 Hz), 5.01 (1H, d, *J* = 11.5 Hz), 2.64 (1H, q, *J* = 7.0 Hz), 2.48 (1H, qd, *J* = 6.5, 6.5 Hz), 2.48-2.38 (1H, m), 2.02-1.97 (1H, m), 1.74-1.60 (6H, m), 1.59-1.53 (2H, m), 1.26-1.17 (3H, m), 1.06 (3H, d, *J* = 7.0 Hz), 0.99 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.8, 136.3, 116.9, 50.9, 40.0, 37.4, 36.7, 32.3, 29.6, 29.4, 26.6, 16.5, 15.8, 13.7; IR (neat): 2967 (w), 2924 (s), 2852 (m), 1709 (s), 1449 (m), 1373 (w), 997 (m), 917 (w); HRMS-(ESI+) for $C_{14}H_{25}O$ $[M+H]^+$: calculated: 209.1905, found: 109.1895.

Proof of Stereochemistry



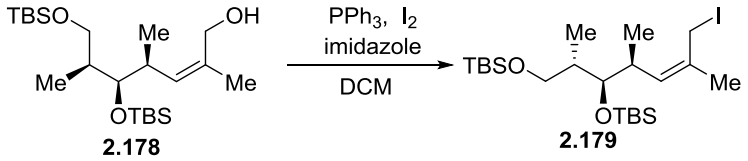
The stereochemistry of **2.177** was proved by making authentic sample **SI-6**. Aldol adduct **SI-5** was prepared following literature procedure as known compound.[134] The spectrum data of **SI-6** (major diastereomer) and **SI-7** were matched.



(2,4-*syn*)-2-Cyclohexyl-4-methylheptan-3-one (SI-6/SI-7). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.60 (1H, tq, *J* = 7.0 Hz), 2.46 (1H, dq, *J* = 7.0Hz), 1.74-1.54 (7H, m), 1,32-1.20 (5H, m), 1.18-1.10 (3H, m), 1.04 (3H, d, *J* = 6.5 Hz), 0.98 (3H, d, *J* = 7.0Hz), 0.89 (3H, t, *J* = 7.5Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.6, 50.9, 40.0, 34.7, 32.3, 29.5, 26.7, 26.6, 26.5, 20.7, 16.7, 14.4, 13.9. IR (neat): 2959 (m), 2925 (s), 2852 (m), 1708 (s), 1449 (m), 1374 (w), 1035 (w), 995 (w); HRMS-(ESI+) for $C_{14}H_{27}O$ $[M+H]^+$: calculated: 211.2062, found: 211.2063. R_f = 0.73 (ethylacetate : hexanes=1:7, stain in $KMnO_4$).

V. C15-C16 Connection

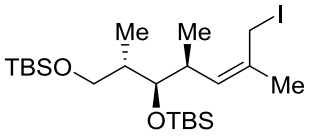
Procedure for Converting Allyl Alcohol to Allyl Iodide



PPh_3 (79.4 mg, 0.3 mmol) and imidazole (22.0 mg, 0.32 mmol) were added to a flame-dried 20-dram vial with stir bar. The vial was purged with nitrogen. Dry CH_2Cl_2 (2.0 mL) was added under nitrogen forming clear solution. I_2 (71.0 mg, 0.28 mmol) was added in one portion at 0 ^{o}C and stirred for 5 min until all I_2 was dissolved resulting light yellow heterogeneous solution. CH_2Cl_2 (2.0 mL) solution of alcohol **2.178** (84.0 mg, 0.20

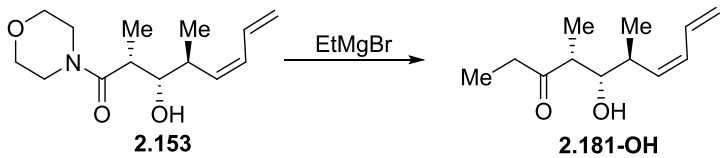
[134] Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48.

mmol) was added dropwise at 0 °C under nitrogen. When reaction completed indicating by TLC (usually in 1 h), all volatiles were removed under reduced pressure and the residue was loaded on silica gel for chromatography to afford corresponding allyl iodide **2.179** as clear colorless oil (105 mg, quantative yield). R_f = 0.76 (diethyl ether: hexanes=1:20, stain in $KMnO_4$).



(5*R*,6*S*)-5-((*S*,*Z*)-5-Iodo-4-methylpent-3-en-2-yl)-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane. (Scheme 2.32, 2.179). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.29 (1H, dd, *J* = 10.0, 1.5 Hz), 3.94 (1H, d, *J* = 9.0 Hz), 3.90 (1H, d, *J* = 9.0 Hz), 3.64 (1H, dd, *J* = 10.5, 6.0 Hz), 3.58 (1H, dd, *J* = 5.5, 5.5 Hz), 3.40 (1H, dd, *J* = 9.5, 7.0 Hz), 2.60 (1H, dqd, *J* = 10.0. 6.5, 6.5 Hz), 1.83 (3H, d, *J* = 1.0 Hz), 1.83-1.81 (1H, m), 0.95 (3H, d, *J* = 6.5 Hz), 0.94 (3H, d, *J* =7.0 Hz), 0.91 (9H, s), 0.90 (9H, s), 0.05 (3H, s), 0.04 (6H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.5, 130.6, 76.5, 65.4, 41.1, 36.2, 26.4, 26.2, 22.6, 18.6, 15.1, 14.0, 7.1, −3.8, −3.9, −5.0, −5.1; IR (neat): 2955 (m), 2928 (m), 2856 (m), 1471 (w), 1387 (w), 1251 (m), 1079 (s), 1023 (m), 834 (s), 772 (s), 670 (w); HRMS-(ESI+) for $C_{22}H_{48}IO_2Si_2$ $[M+H]^+$: calculated: 527.2238, found: 527.2242. $[\alpha]_D^{21}$ = +17.284 (*c* = 1.40, $CHCl_3$, *l* = 50 mm).

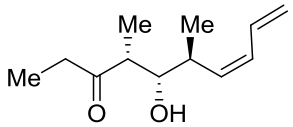
Procedure for the Alkylation of Morpholine Amide



2.153 **2.181-OH**

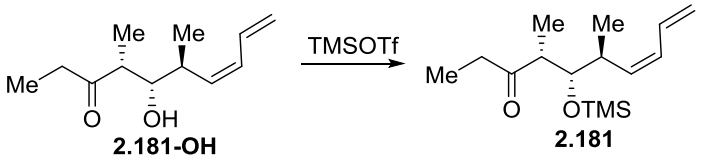
β–hydroxymorpholine amide **2.153** (200 mg, 0.8 mmol) was dissolved in dry THF

(8.0 mL) in a round bottom flask equipped with magnetic stir bar under nitrogen. Ethyl magnesium bromide (3.0 M in Et_2O, 1.1 mL, 3.3 mmol) was added dropwise at 0 ^oC. It was allowed to warm to room temperature slowly and stirred overnight. Reaction was quenched by slow addition of 1.0 M HCl aqueous solution on ice bath. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (1:5 hexanes:diethyl ether) to afford the titled compound **2.181-OH** as a clear, colorless oil (120 mg, 77%). R_f = 0.37 (1:5 hexanes:ethyl acetate, stain in $KMnO_4$).

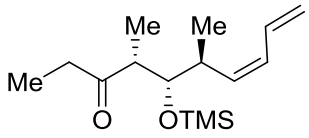


(4*R*,5*S*,6*S*,*Z*)-5-Hydroxy-4,6-dimethyldeca-7,9-dien-3-one (Scheme 2.32, 2.181-OH). ^1H NMR (500 MHz, $CDCl_3$): δ 6.54 (1H, dt, *J* = 16.5, 10.5 Hz), 6.11 (1H, t, *J* = 10.5 Hz), 5.39 (1H, t, *J* = 10.5 Hz), 5.22 (1H, dt, *J* = 16.5, 1.0 Hz), 5.12 (1H, d, *J* = 10.0 Hz), 3.74-3.72 (1H, m), 2.74 (1H, dqd, *J* = 10.5, 6.5, 6.5 Hz), 2.67 (1H, dq, *J* = 9.0, 7,5 Hz), 2.54 (1H, dqd, *J* = 18.0, 7.5, 7.5 Hz), 2.45 (1H, dqd, *J* = 18.0, 7.5, 7.5 Hz), 2.23 (1H, br, s), 1.16 (3H, d, *J* = 7.5 Hz), 1.03 (3H, t, *J* = 7.0 Hz), 0.99 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.6, 134.1, 132.2, 130.7, 118.4, 75.4, 48.4, 35.7, 35.0, 17.8, 10.9, 7.8; IR (neat): 3505 (m), 2970 (m), 2932 (m), 2876 (w), 1705 (s), 1458 (m), 1376 (m), 1144 (w), 974 (s), 905 (m), 805 (m); HRMS-(ESI+) for $C_{14}H_{21}O_2$ $[M+H]^+$: calculated: 197.1542, found: 197.1542. $[\alpha]_D^{21}$ = +34.145 (*c* = 0.48, $CHCl_3$, *l* = 50 mm).

Procedure for Trimethylsilyl Protection



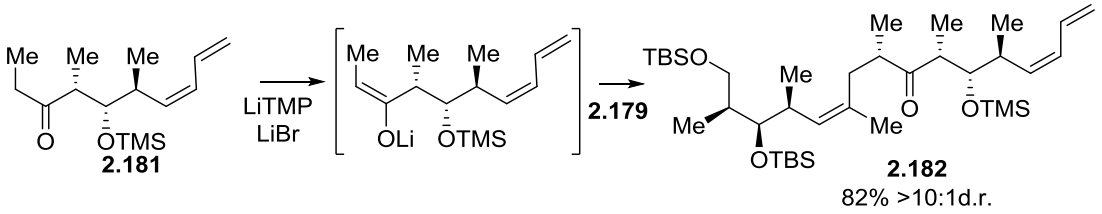
A flame-dried round-bottom flask containing magnetic stir bar was charged with alcohol **2.181-OH** (100.0 mg, 0.50 mmol) in CH_2Cl_2 (5 mL) and 2,6-lutidine (0.09 mL, 0.77 mmol) under nitrogen. The reaction flask was cooled to −78 °C, followed by dropwise addition of freshly distilled TMSOTf (0.11 mL, 0.61 mmol). The reaction was allowed to stir for 1 h until TLC showed full conversion of starting material. Reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by triethylamine neutralized silica gel chromatography (100:1:1 hexanes:diethyl ether:triethylamine) to afford **2.181** as a clear, colorless oil (130 mg, 97%). R_f = 0.40 (diethyl ether:hexanes=1:20, stain in $KMnO_4$)



(4*R*,5*S*,6*S*,*Z*)-4,6-Dimethyl-5-((trimethylsilyl)oxy)deca-7,9-dien-3-one (Scheme 2.32, 2.181). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.42 (1H, dt, *J* = 16.5, 11.0 Hz), 6.03 (1H, t, *J* = 11.0 Hz), 5.49 (1H, t, *J* = 10.5 Hz), 5.18 (1H, dt, *J* = 16.5, 1.0 Hz), 5.08 (1H, d, *J* = 10.0 Hz), 3.86 (1H, dd, *J* = 8.5, 3.0 Hz), 2.67-2.61 (2H, m), 2.47 (1H, dqd, *J* = 18.5, 7.5, 7.5 Hz), 2.37 (1H, dqd, *J* = 18.5, 7.5, 7.5 Hz), 1.08 (3H, d, *J* = 7.0 Hz), 0.99 (3H, t, *J* = 7.5 Hz), 0.98 (3H, t, *J* = 7.5 Hz), 0.13 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.1, 134.0, 132.4, 129.7, 117.7, 78.0, 50.9, 36.4, 36.1, 19.3, 15.0, 7.6, 1.0; IR (neat): 2962 (m), 2937 (w), 1710 (s), 1377 (m),

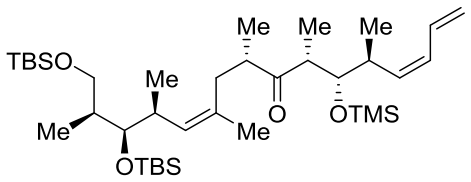
1250 (s), 1135 (m), 1075 (s), 1025 (s), 883 (s), 835 (s), 749 (s), 684 (m); HRMS-(ESI+) for $C_{15}H_{29}O_2Si$ $[M+H]^+$: calculated: 269.1937, found: 269.1933. $[\alpha]_D^{21}$ = +18.674 (*c* = 0.34, $CHCl_3$, *l* = 50 mm).

Procedure for Enolate Alkylation Construct C15-C16 Bond



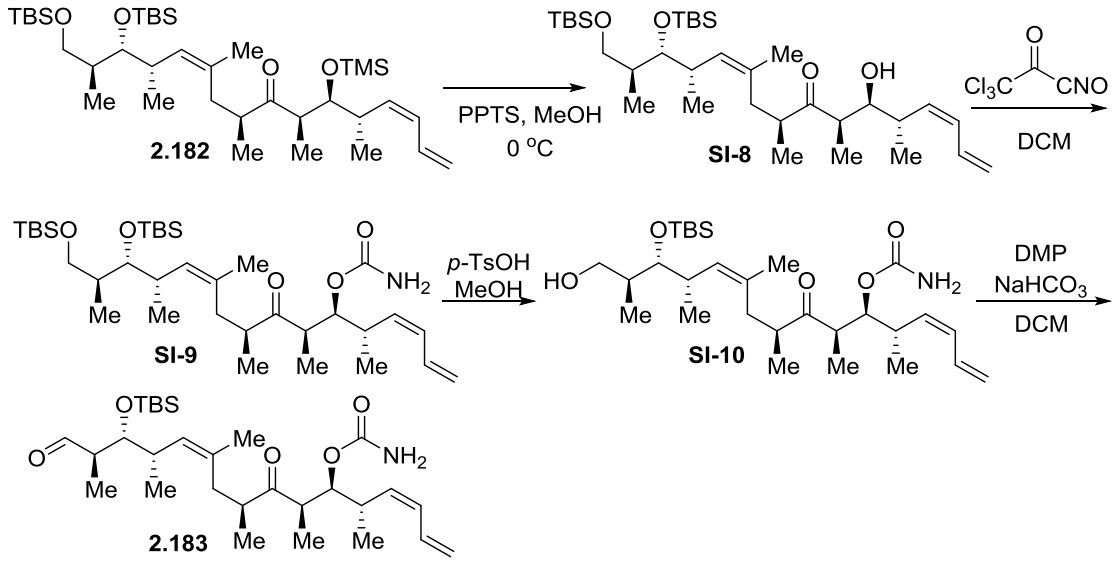
Enolate alkylation general procedure was used. To a rapidly stirred suspension of TMP·HBr (50 mg, 0.224 mmol) and a spatula-tip of 1,10-phenanthroline in THF (3.0 mL) at 0 °C under nitrogen was added 2.5 M solution of *n*-BuLi in hexanes dropwise until deep red color persists as well as no solid left at bottom. Then a 0.95 equiv. of *n*-BuLi as previously added was transferred to the dark red solution dropwise. After being stirred for an additional 5 min at 0 °C, the resulting dark red solution was cooled to −78 °C and ethyl ketone **2.181** (60 mg, 0.224 mmol) was added as THF (0.8 mL) solution dropwise. Such solution was stirred at −78 °C for 30 min. A THF (1.0 mL) solution of allyl iodide **2.179** (130 mg, 0.246 mmol) was added dropwise at −78 °C and stirred overnight until TLC showed full conversion of ethyl ketone. Reaction was quenched with aqueous NH_4Cl and allowed to warm to room temperature. The reaction mixture was diluted with ethyl acetate and layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. Diastereoselectivity was determined by ^1H NMR. The crude was purified through triethylamine neutralized silica gel chromatography

(Et_2O:TEA:hexanes = 1:1:100) to afford titled compound **2.182** as light yellow oil (120 mg, 81% yield, >10:1 d.r.). R_f = 0.58 (diethyl ether:hexanes=1:20, stain in $KMnO_4$).

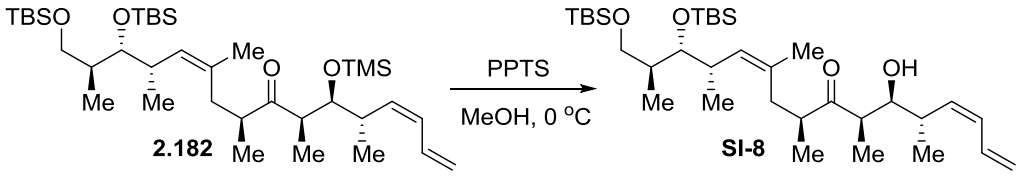


(4*S*,5*R*,7*S*,11*S*,12*R*,13*S*,*Z*)-12-((*tert*-Butyldimethylsilyl)oxy)-4-((*S*,*Z*)-hexa-3,5-dien-2-yl)-2,2,5,7,9,11,13,16,16,17,17-undecamethyl-3,15-dioxa-2,16-disilaoctadec-9-en-6-one (Scheme 2.33, 2.182). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.44 (1H, dt, *J* = 17.0, 11.5 Hz), 6.03 (1H, t, *J* = 11.0 Hz), 5.59 (1H, t, *J* = 10.5 Hz), 5.17 (1H, d, *J* = 16.5 Hz), 5.15 (1H, d, *J* = 9.5 Hz), 5.06 (1H, d, *J* = 10.0 Hz), 3.88 (1H, dd, *J* = 8.0, 2.5 Hz), 3.63 (1H, dd, *J* = 10.0, 5.5 Hz), 3.41 (1H, dqd, *J* = 11.0, 7.5, 7.5 Hz), 3.34 (1H, dd, *J* = 9.5, 7.5 Hz), 2.79 (1H, qd, *J* = 7.0 Hz), 2.68 (1H, dqd, *J* = 11.0, 7.5, 7.5 Hz), 2.61-2.58 (1H, m), 2.51 (1H, dqd, *J* = 10.0, 5.5, 5.5 Hz), 2.20 (1H, dd, *J* = 13.0, 11.0 Hz), 2.00 (1H, dd, *J* = 13.0, 3.0 Hz), 1.82-1.77 (1H, m), 1.58 (3H, s), 1.11 (3H, d, *J* = 7.5 Hz), 1.00 (3H, d, *J* = 6.5 Hz), 0.96 (3H, d, *J* = 6.5 Hz), 0.89 (3H, d, *J* = 5.5 Hz), 0.88 (3H, d, *J* = 6.5 Hz), 0.91 (9H, s), 0.89 (9H, s), 0.14 (9H, s), 0.03 (9H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.2, 133.6, 133.4, 132.6, 130.1, 130.0, 118.0, 77.8, 77.6, 65.7, 50.1, 43.9, 41.3, 36.7, 35.3, 34.2, 26.4, 26.2, 23.3, 19.9, 18.6, 18.5, 16.5, 15.4, 15.3, 14.0, 1.1, −3.7, −3.8, −5.0, −5.1 (δ 31.8, 22.9, 14.3 belong to hexanes); IR (neat): 2957 (m), 2929 (m), 2856 (m), 1707 (w), 1471 (w), 1251 (s), 1078 (s), 1023 (s), 1001 (s), 834 (s), 772 (s), 670 (w); HRMS-(ESI+) for $C_{37}H_{74}O_4NaSi_3$ $[M+Na]^+$: calculated: 689.4787, found: 689.4778. $[\alpha]_D^{21}$ = +3.172 (*c* = 0.52, $CHCl_3$, *l* = 50 mm).

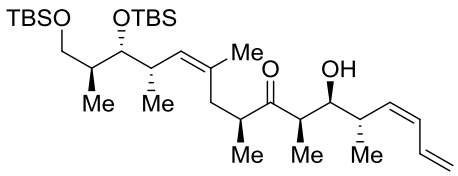
VI. Preparation of Aldehyde for Still-Gennari Olefination



Procedure for Removal of Trimethylsilyl Protecting Group

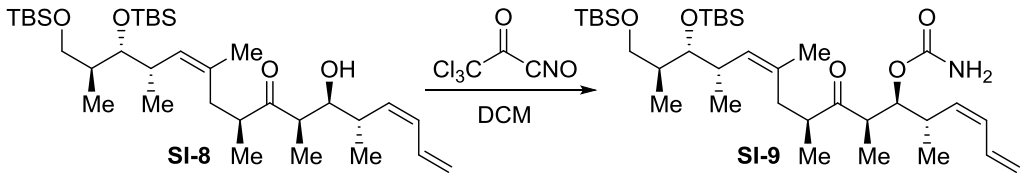


Ketone **2.182** (30.0 mg, 0.045 mmol) was dissolved in 1.0 mL MeOH and cooled to 0 °C. Several crystalline of PPTS were added to the solution and stirred at 0 °C. The reaction was monitored by TLC carefully. Once reaction was completed, all volatiles were removed under reduced pressure. Residue was purified immediately by silica gel chromatography to afford **SI-8** as a clear colorless oil (26.0mg, 96% yield). R_f = 0.68 (ethylacetate:hexanes=1:3, stain in $KMnO_4$) .



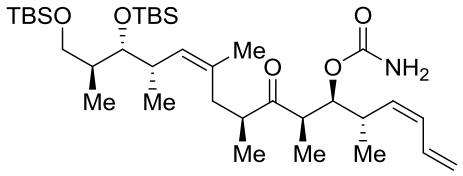
(3*Z*,5*S*,6*S*,7*R*,9*S*,11*Z*,13*S*,14*R*,15*S*)-14,16-Bis((*tert*-butyldimethylsilyl)oxy)-6-hydroxy-5,7,9,11,13,15-hexamethylhexadeca-1,3,11-trien-8-one. (SI-8). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.59 (1H, dt, *J* = 17.5, 9.5 Hz), 6.11 (1H, t, *J* = 11.0Hz), 5.43 (1H, t, *J* = 10.0 Hz), 5.23 (1H, d, *J* = 16.5 Hz), 5.18 (1H, d, *J* = 10.0 Hz), 5.13 (1H, d, *J* = 9.5 Hz), 3.71 (1H, dd, *J* = 7.5, 3.5 Hz), 3.63 (1H, dd, *J* = 10.0, 5.0 Hz), 3.42 (1H, dd, *J* = 5.5, 5.5 Hz), 3.35 (1H, dd, 9.5, 7.5 Hz), 2.86-2.81 (2H, m), 2.75 (1H, dqd, *J* = 10.0, 7.0, 7.0 Hz), 2.52 (1H, dqd, *J* = 10.5, 6.0, 6.0 Hz), 2.24 (1H, dd, *J* = 13.5, 9.5 Hz), 2.07 (1H, dd, *J* = 13.0, 4.5), 1.79 (1H, qd, *J* = 9.5, 9.5 Hz), 1.63 (3H, s), 1.18 (3H, d, *J* = 7.5 Hz), 0.95 (3H, d, *J* = 6.5 Hz), 0.99 (3H, d, *J* = 6.0 Hz),, 0.91 (3H, d, overlap), 0.90 (9H, s), 0.90 (3H, d, overlap), 0.89 (9H, s), 0.04 (3H, s), 0.03 (6H, s), 0.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 218.7, 134.5, 133.5, 132.3, 130.5, 130.0, 118.4, 77.8, 74.9, 65.6, 47.1, 43.2, 41.2, 35.6, 35.4, 35.2, 26.4, 26.2, 25.9, 23.6, 18.6, 18.5, 17.8, 16.6, 15.8, 14.1, 10.3, −3.6, −3.7, −5.1; IR (neat): 3496 (w), 2957 (s), 2929 (s), 2856 (s), 1701 (m), 1460 (s), 1374 (m), 1251 (s), 1080 (s), 1022 (s), 833 (s), 772 (s), 667 (m); HRMS-(ESI+) for $C_{38}H_{67}OSi_2$ $[M+H]^+$: calculated: 689.4787, found: 689.4778. $[\alpha]_D^{21}$ = +28.102 (*c* = 0.66, $CHCl_3$, *l* = 50 mm).

Procedure for Installation of Primary Carbamate



To a CH_2Cl_2 (1.0 mL) solution of alcohol **SI-8** (26 mg, 0.045 mmol) was added trichloroacetyl isocyanate (34 μL) under nitrogen at room temperature. After one hour of

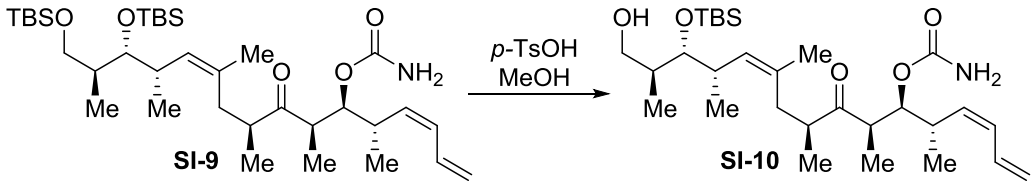
stirring, neutral alumina (1.2 g) was added. After stirring vigorously for an additional 4 hours, the reaction mixture was concentrated. Residue (adsorbed on the alumina) was placed on the top of silica gel column, and was purified by flash chromatography to give the titled compound **SI-9** as a clear oil (28 mg, 97% yield). R_f = 0.48 (ethyl acetate: hexanes=1:3, stain in $KMnO_4$).



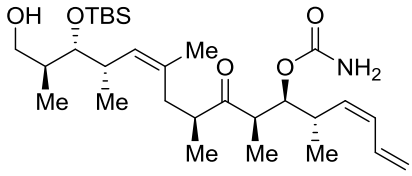
(3*Z*,5*S*,6*S*,7*R*,9*S*,11*Z*,13*S*,14*R*,15*S*)-14,16-Bis((*tert*-butyldimethylsilyl)oxy)-5,7,9,11,13,15-hexamethyl-8-oxohexadeca-1,3,11-trien-6-yl carbamate (SI-9). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.48 (1H, dt, *J* = 16.5, 10.0 Hz), 6.05 (1H, t, *J* = 11.0 Hz), 5.43 (1H, t, *J* = 11.0 Hz), 5.20 (1H, d, *J* = 16.0 Hz), 5.15 (1H, d, *J* = 10.5 Hz), 5.10 (1H, d, *J* = 9.5 Hz), 5.09 (1H, d, *J* = 10.5 Hz), 4.62 (2H, br, s), 3.62 (1H, dd, *J* = 10.0, 5.5 Hz), 3.41 (1H, dd, *J* = 5.0, 5.0 Hz), 3.33 (1H, dd, *J* = 10.0, 8.0 Hz), 2.95 (1H, qd, *J* = 7.5, 7.5 Hz), 2.90-2.86 (1H, m), 2.77 (1H, dqd, *J* = 7.0, 7.0, 3.5 Hz), 2.50 (1H, dqd, *J* = 6.5, 6.5, 3.5 Hz), 2.42 (1H, dd, *J* = 13.5, 11.5 Hz), 1.99 (1H, dd, *J* = 13.5, 2.5 Hz), 1.79 (1H, qd, *J* = 5.5 Hz), 1.60 (3H, s), 1.13 (3H, d, *J* = 6.5 Hz), 1.03 (3H, d, *J* = 6.0 Hz), 0.97 (3H, d, *J* = 7.0 Hz), 0.90 (9H, s), 0.89 (9H, s), 0.88 (3H, d, overlap), 0.87 (3H, d, overlap), 0.03 (9H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.7, 156.5, 133.4, 132.5, 131.9 ,130.5, 129.9, 118.4, 77.6, 76.8, 65.5., 47.0, 42.7, 41.1, 35.1, 34.7, 33.9, 26.2, 26.0, 23.1, 18.4, 18.3, 18.0, 16.4, 15.4, 13.7, 12.5, −3.9, −4.0, −5.2, −5.3; IR (neat): 2957 (m), 2929 (m), 2856 (m), 1708 (s), 1600 9w), 1471 (m), 1387 (m), 1323 (m), 1252 (m), 1079 (m), 1003 (s), 834 9s), 772 (s), 667 (w); HRMS-(ESI+) for $C_{35}H_{68}NO_5Si_2$

$[M+H]^+$: calculated: 638.4630, found: 638.4665. $[\alpha]_D^{21}$ = +27.497 (*c* = 0.40, $CHCl_3$, *l* = 50 mm).

Procedure for Selective Removal of Primary TBS Protecting Group



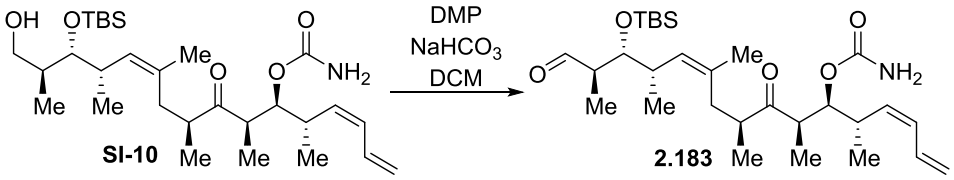
bis-TBS ether **SI-9** (26 mg, 0.041 mmol) was dissolved in methanol (1.0 mL) and cooled to 0 ^oC. Several crystalline of *p*-TsOH were added to the solution and stirred at 0 ^oC. The reaction was monitored by TLC carefully. Once it showed full consumption of starting material, triethylamine (1.0 mL) was added to quench the reaction. All volatiles were removed under reduced pressure. Residue was purified immediately *via* silica gel chromatography to afford titled compound **SI-10** as clear colorless oil (20 mg, 93%). R_f = 0.29, (ethylacetate:hexanes=1:3, stain in $KMnO_4$).



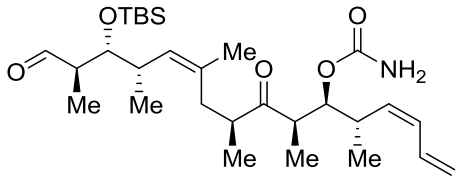
(3*Z*,5*S*,6*S*,7*R*,9*S*,11*Z*,13*S*,14*R*,15*S*)-14-((*tert*-Butyldimethylsilyl)oxy)-16-hydroxy-5,7,9,11,13,15-hexamethyl-8-oxohexadeca-1,3,11-trien-6-yl carbamate (SI-10). ^1H NMR (500 MHz, $CDCl_3$): δ 6.49 (1H, dt, *J* = 17.5, 11.0 Hz), 6.05 (1H, t, *J* = 10.5 Hz), 5.41 (1H, t, *J* = 10.0 Hz), 5.21 (1H, d, *J* = 17.5 Hz), 5.12-5.06 (2H, m), 4.64 (2H, br, s), 3.62 (1H, dd, *J* = 11.0, 5.0 Hz), 3.56 (1H, dd, *J* = 11.0, 5.5 Hz), 3.40 (1H, dd, *J* = 6.0, 4.0 Hz), 2.95 (1H, qd, *J* = 7.5 Hz), 2.93-2.86 (1H, m), 2.82 (1H, dqd, *J* = 14.0, 7.0, 7.0 Hz), 2.60 (1H, dqd, *J* = 10.5, 6.5, 6.5 Hz), 2.23 (1H, dd, *J* = 13.5, 11.0

Hz), 2.5 (1H, dd, J = 14.0, 3.0 Hz), 1.83-1.78 (1H, m), 1.62 (3H, s), 1.13 (3H, d, J = 7.0 Hz), 1.03 (3H, d, J = 7.0 Hz), 0.98 (6H, d, J = 7.5 Hz overlap), 0.92 (3H, d, J = 7.0 Hz), 0.92 (9H, s), 0.09 (3H, s), 0.06 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.9, 156.7, 132.8, 132.3, 132.2, 131.4, 130.7, 118.6, 81.5, 65.6, 47.1, 42.7, 38.7, 36.9, 34.9, 34.2, 26.4, 23.3, 18.6, 18.2, 17.4, 16.1, 15.9, 12.3, −3.4, −3.7; IR (neat): 3664 (m), 2963 (s), 2856 (s), 1712 (s), 1601 (m), 1460 (m), 1361 (m), 1324 (s), 1254 (m), 1026 (s), 1003 (s), 836 (s), 774 (s); HRMS-(ESI+) for $C_{29}H_{54}NO_5Si$ $[M+H]^+$: calculated: 524.3771, found: 524.3798. $[\alpha]_D^{21}$ = +19.997 (c = 0.34, $CHCl_3$, l = 50 mm).

Procedure for Dess-Martin Oxidation of Alcohol

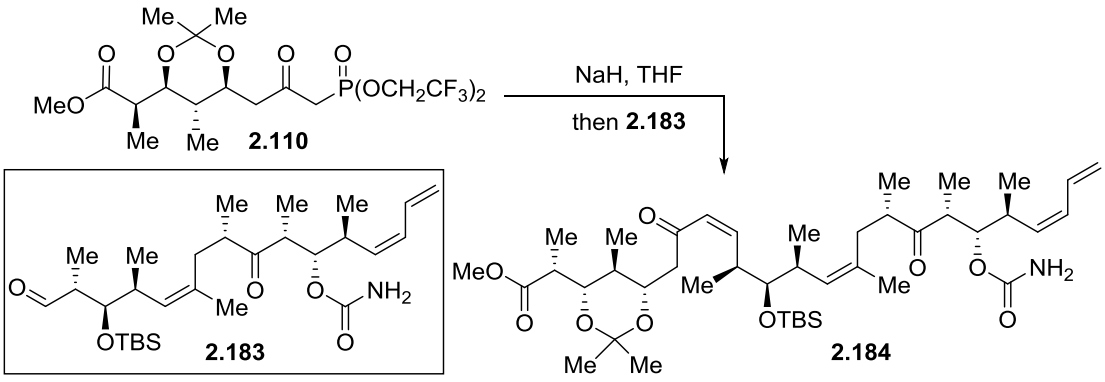


A CH_2Cl_2 (1.0 mL) solution of alcohol **SI-10** (20 mg, 0.038 mmol) was added to a 20-dram vial with $NaHCO_3$ (38 mg, 0.456 mmol) and Dess-Martin periodinane (19.0 mg, 0.046 mmol) at room temperature under nitrogen and stirred for 4 hours to reach full conversion. Et_2O (4.0 mL), saturated aqueous $NaHCO_3$ (2.0 mL), and $Na_2S_2O_3$ (2.0 mL) were added and allowed to stir vigorously for 15 minutes. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography to afford titled aldehyde **2.183** as colorless oil (18 mg, 92% yield). R_f = 0.48 (ethylacetate:hexanes=1:3, stain in $KMnO_4$).



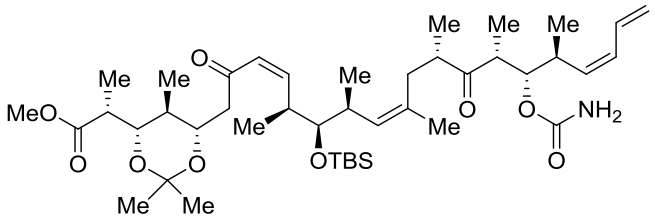
(3*Z*,5*S*,6*S*,7*R*,9*S*,11*Z*,13*S*,14*R*,15*R*)-14-((*tert*-Butyldimethylsilyl)oxy)-5,7,9,11,13,15-hexamethyl-8,16-dioxohexadeca-1,3,11-trien-6-yl carbamate. (Scheme 2.33, 2.183). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.62 (1H, d, *J* = 1.5 Hz), 6.49 (1H, dt, *J* = 16.5, 10.5 Hz), 6.06 (1H, t, *J* = 11.5 Hz), 5.42 (1H, t, *J* = 10.5 Hz), 5.21 (1H, dd, *J* = 17.0, 1.0 Hz), 5.11 (1H, dd, *J* = 16.0, 10.0 Hz), 4.92 (1H, d, *J* = 10.5 Hz), 4.58 (2H, br, s), 3.75-3.73 (2H, m), 2.96 (1H, qd, *J* = 7.0, 7.0 Hz), 2.92-2.89 (1H, m), 2.79 (1H, dqd, *J* = 7.5, 7.5, 4.0 Hz), 2.59 (1H, dqd, *J* = 10.5, 7.0 Hz), 2.52-2.47 (1H, m), 2.26 (1H, dd, *J* = 13.5, 11.0 Hz), 1.97 (1H, dd, *J* = 11.0, 3.0 Hz), 1.59 (3H, s), 1.14 (3H, d, *J* = 7.0 Hz), 1.08 (3H, d, *J* = 6.5 Hz), 1.04 (3H, d, *J* = 6.5 Hz), 0.96 (3H, d, *J* = 6.5 Hz), 0.95 (3H, d, *J* = 6.5 Hz), 0.90 (9H, s), 0.08 (3H, s), 0.06 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.7, 203.6, 156.7, 133.6, 132.7, 132.1, 131.6, 131.0, 130.7, 118.7, 78.6, 77.6, 51.9, 47.1, 36.6, 34.8, 34.4, 26.1, 23.1, 18.4, 18.2, 17.0, 15.7, 12.6, 10.3, −3.9, −4.0; IR (neat): 2960 (m), 2929 (m), 2856 (m), 1711 (s), 1598 (w), 1459 (m), 1360 (m), 1322 (m), 1253 (m), 1037 (s), 1002 (s), 08 (m), 836 (s), 774 (s), 732 (m), 670 (m); HRMS-(ESI+) for $C_{29}H_{51}NO_5NaSi$ $[M+Na]^+$: calculated: 544.3434, found: 544.3438. $[\alpha]_D^{21}$ = +15.598 (*c* = 0.20, $CHCl_3$, *l* = 50 mm).

VII. Still-Gennari Olefination and End Game



NaH (1.2 mg, 0.051 mmol) was suspended in dry THF (1.0 mL) in a flame dried 10-dram vial with septa in glove box. The vial was brought out of box and cooled to −10 ^{o}C. A THF (2.0 mL) solution of β-keto-phosphonate **2.110** (28.0 mg, 0.054 mmol) that was freshly purified via silica gel chromatography and azeotropically dried with benzene was cannula transferred to the vial dropwise at −10 ^{o}C. Such mixture was allowed to stir another 40 min at −10 ^{o}C resulted a light yellow and homogeneous solution. Then the vial was cooled to −20 ^{o}C. A THF (1.0 mL) solution of aldehyde **2.183** (14.0 mg, 0.027 mmol) that was freshly purified via silica gel chromatography and azeotropically dried with benzene was added to the light yellow solution at −20 ^{o}C dropwise, and the reaction mixture was allowed to warm to room temperature slowly and stirred for another 24 h until TLC showed full consumption of aldehyde. The reaction was quenched with aqueous NH_4Cl and layers were separated. The aqueous phase was extracted with ethylacetate (3 × 15 mL). The organic layers were combined and dried over Na_2SO_4, concentrated under reduced pressure. The *Z*:*E* ratio was determined by ^{1}H NMR as being 4.3:1. The residue was purified by flash chromatography to afford pure (*Z*)-olefin as a colorless oil (18.6 mg, 63%). R_f = 0.31 (ethylacetate:hexanes=1:3, stain in $KMnO_4$). For

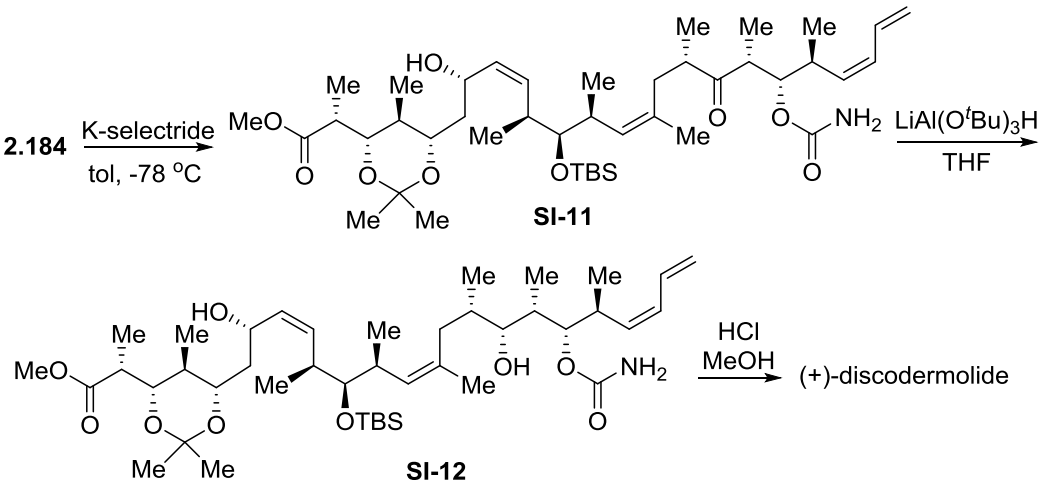
(*E*)-isomer, R_f = 0.23 (ethylacetate:hexanes=1:3, stain in $KMnO_4$). These two isomers were easily separated through silica gel chromatography.



Methyl-(*R*)-2-((4*S*,5*S*,6*S*)-6-((3*Z*,5*S*,6*S*,7*S*,8*Z*,11*S*,13*R*,14*S*,15*S*,16*Z*)-6-((*tert*-butyldimethylsilyl)oxy)-14-(carbamoyloxy)-5,7,9,11,13,15-hexamethyl-2,12-dioxononadeca-3,8,16,18-tetraen-1-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoate (Scheme 2.33, 2.184). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.50 (1H, dt, *J* = 16.5, 11.0 Hz), 6.23 (1H, dd, *J* = 11.5, 9.5 Hz), 6.12 (1H, d, *J* = 11.5 Hz), 6.05 (1H, t, *J* = 10.5 Hz), 5.41 (1H, t, *J* = 11.0 Hz), 5.21 (1H, d, *J* = 17.0 Hz), 5.11 (1H, d, *J* = 10.0 Hz), 5.07 (1H, t, *J* = 6.5 Hz), 4.96 (1H, d, *J* = 10. Hz), 4.61 (2H, br, s), 4.13-4.07 (2H, m), 3.68 (3H, s), 3.61 (1H, t, *J* = 7.0 Hz), 3.39 (1H, dd, *J* = 7.0, 3.0 Hz), 2.95 (1H, qd, *J* = 6.0, 6.0 Hz), 2.88 (1H, dqd, *J* = 10.5, 6.0, 6.0 Hz), 2.79-2.72 (1H, m), 2.70-2.65 (2H, m), 2.56 (1H, dd, *J* = 16.0, 7.5 Hz), 2.37 (1H, dqd, *J* = 10.0, 7.0, 7.0 Hz), 2.25 (1H, t, *J* = 11.5 Hz), 1.85 (1H, d, *J* = 11.5 Hz), 1.60-1.57 (1H, m), 1.57 (3H, s), 1.45-1.41 (1H, m), 1.41 (3H, s), 1.30-1.25 (2H, m), 1.27 (3H, s), 1.12 (3H, d, *J* = 6.5 Hz), 1.15 (3H, d, *J* = 7.0 Hz), 1.03 (3H, d, *J* = 7.0 Hz), 0.99 (3H, d, *J* = 7.0 Hz), 0.93 (3H, d, *J* = 7.5 Hz), 0.92 (9H, s), 0.88 (3H, d, *J* = 7.0 Hz), 0.76 (3H, d, *J* = 7.0 Hz), 0.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.0, 199.0, 175.1, 156.5, 151.5, 132.9, 132.2, 132.1, 131.3, 130.7, 128.6, 125.8, 118.5, 98.5, 80.6, 77.5, 74.8, 71.6, 51.9, 48.7, 46.8, 42.6, 41.0, 37.8, 37.7, 36.2, 34.9, 34.1, 30.0, 26.4, 26.3, 23.1, 19.5, 18.7, 18.1, 15.8, 12.1, 12.0, 8.8, −3.4, −3.5; IR (neat): 2964 (m), 2930 (m), 2856 (w), 1734 (s), 1459 (m), 1360 (m), 1321 (m), 1257 (m), 1207 (m), 1038

(m), 836 (w), 798 (w); HRMS-(ESI+) for $C_{43}H_{73}NO_9NaSi$ $[M+Na]^+$: calculated: 798.4952, found: 798.4952. $[\alpha]_D^{21}$ = +53.858 (*c* = 0.22, $CHCl_3$, *l* = 50 mm).

Procedure for Sequential Reduction of bis-Ketone

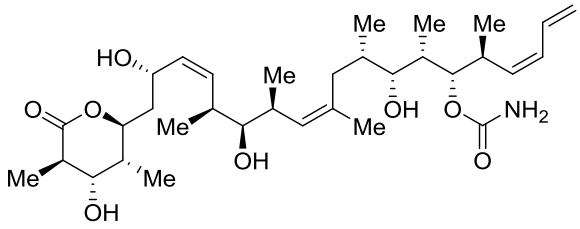


Following literature procedure[18d,100]**Error! Bookmark not defined.** with slightly modification, bis-ketone **2.184** (7.0 mg, 10 µmol) was dissolved in toluene (1.0 mL) and cooled to −78°C under nitrogen. K-Selectride® (1M in THF, 20 µL, 20 µmol) was added dropwise, and the reaction mixture was stirred for 3 h at −78°C. The mixture was quenched with water (2 mL) and THF (2.0 mL). Sodium perborate (20 mg, 0.2 mmol) was added. The mixture was stirred vigorously at room temperature for 1h. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). Combined organic layers were dried over $NaSO_4$ and concentrated. The residue was passed through a plug of silica gel with ethyl acetate and used for next step without further purification. R_f = 0.63 (ethyl acetate: hexane=1:1).

Following literature procedure[18d] with slightly modification, the alcohol **SI-11** was dissolved in dry THF (1.0 mL) and cooled to 0 °C in a 20-dram vial. Li(O*t*-Bu)$_3$AlH

(1M in THF, 50 μL, 50 μmol) was added dropwise at 0 °C and the mixture was allowed to warm to room temperature slowly and stirred for additional 2 h. Aqueous NH_4Cl (0.3 mL) was added to quench reaction and stirred for 2 h at room temperature. A spatula of $MgSO_4$ was added to the vial to remove water. The residue was directly loaded on the top of a plug of silica gel and flashed with ethyl acetate, and concentrated under reduced pressure. The crude diol **SI-12** was used for next step without further purification. R_f = 0.41 (ethyl acetate:hexane=1:1).

The diol **SI-12** was dissolve in MeOH (1.0 mL) in 20 dram vial and cooled to 0 °C. 3 M aqueous HCl (0.5 mL) was added dropwise and the mixture was allowed to warm to room temperature and stir for 24 h until TLC showed full conversion of starting material. Aqueous $NaHCO_3$ was added carefully until bubbling ceased. The layers were separated and the aqueous phase was extracted with ethyl acetate (5 × 5 mL), combined organic layers were dried over $NaSO_4$ and concentrated. The residue was purified through silica gel (MeOH: CH_2Cl_2=1:20 to 1:10) to afford (+)-discodermolide **2.1** as white solid (4.5 mg, 76% over three steps).

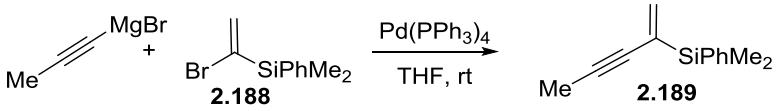


(+)-Discodermolide (2.1). All spectrum data are in accordance with literature reports. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.62 (1H, dt, *J* = 16.5, 10.0 Hz), 6.04 (1H, t, *J* = 11.0 Hz), 5.53 (1H, dd, *J* = 11.5, 8.0 Hz), 5.43 (1H, dd, *J* = 10.5, 10.5 Hz), 5.36 (1H, dd, *J* = 11.0, 11.0 Hz), 5.22 (1H, d, *J* = 17.0 Hz), 5.18 (1H, d, 15.5 Hz), 5.12 (1H, d, *J* = 10.0 Hz), 4.75 (1H, ddd, *J* = 7.5, 7.5, 2.5 Hz), 4.71 (1H, dd, *J* =7.5, 4.5 Hz), 4.62 (1H,

ddd, J = 10.5, 10.5 Hz), 4.61 (2H, br, s), 3.75 (1H, d, J = 3.5 Hz), 3.29 (1H, dd, J = 4.5, 4.5 Hz), 3.20 (1H, dd, 7.0, 5.0 Hz), 3.00 (1H, ddq, J = 10.0, 7.0, 7.0 Hz), 2.80 (1H, ddq, J = 10.0, 7.0, 7.0 Hz), 2.68 (1H, dq, J = 1H, dq, J = 7.5, 4.5 Hz), 2.62-2.58 (1H, m), 2.02-1.80 (10H, m), 1.74-1.67 (1H, m), 1.65 (3H, s), 1.32 (3H, d, J = 7.5 Hz), 1.08 (3H, d, J = 7.0 Hz), 1.02 (3H, d, J = 6.0 Hz), 1.00 (3H, d, J = 6.0 Hz), 0.95 (3H, d, J = 6.5 Hz), 0.83 (3H, d, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 157.3, 134.6, 133.9, 133.7, 133.1, 132.4, 130.1, 129.9, 118.2, 79.2, 79.1, 77.4, 75.9, 73.4, 64.6, 43.3, 41.2, 37.6, 36.3, 36.2, 36.0, 35.5, 35.0, 33.3, 23.5, 18.6, 17.7, 15.9, 15.8, 13.9, 12.8, 9.2; HRMS-(ESI+) for $C_{33}H_{55}NO_8Na$ $[M+Na]^+$: calculated: 616.3825, found: 616.3527. $[\alpha]_D^{21}$ = +6.794 (c = 0.20, MeOH, l = 50 mm), literature[5]: $[\alpha]_D^{21}$ = +7.2 (c = 0.72, MeOH).

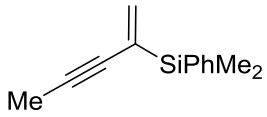
VIII. Synthesis of Oxidation Resistant Analog

Preparation of Silicon Substituted Enyne



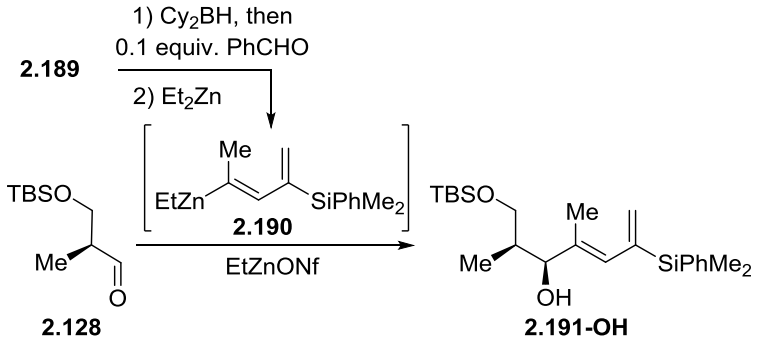
$Pd(PPh_3)_4$ (96 mg, 0.083 mmol) and vinyl bromide **2.188** (1.0 g, 4.15 mmol) was added to a flame dried round bottom flask with stir bar. Then a THF solution of propynyl magnesium bromide (0.5 M, 16.7 mL, 8.3 mmol) was added to the flask under N_2 slowly at room temperature result a clear solution, which was allowed to stir overnight. The reaction was carefully quenched with NH_4Cl (a.q.). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography to afford **2.189** as colorless oil (750 mg, 90% yield). R_f

= 0.18 (hexanes, stain in $KMnO_4$).



Dimethyl(pent-1-en-3-yn-2-yl)(phenyl)silane (Scheme 2.34, 2.189). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.56 (2H, m), 7.36 (3H, m), 6.09 (1H, d, *J* = 3.0 Hz), 5.60 (1H, d, *J* = 2.5 Hz), 1.97 (3H, s), 0.43 (6H, s), 0.33 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.8, 134.2, 133.2, 129.5, 128.0, 127.9, 81.1, 4.7, 1.1, −3.2.

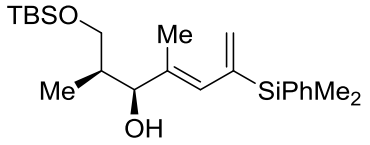
Preparation of Silicon Substituted Chiral Dienol



Preparation of EtZnONf: To a flame-dried 25 mL Schlenk flask equipped with magnetic stir bar and septum was added Et_2Zn (0.9 mL, 1.8 mmol, 2 M in CH_2Cl_2). The solution was cooled to –78 °C in a dry ice/acetone bath, and nonafluorobutane-1-sulfonic acid (0.23 mL, 1.5 mmol) was added dropwise. The reaction was allowed to stir at –78 °C for 5 min and was allowed to warm to room temperature and stirred for 1 h resulting white slurry.

$HBCy_2$ (213 mg, 1.2 mmol) and CH_2Cl_2 (1.2 mL) was added to a flame dried 100 mL two-neck round bottom flask in glove box. The flask was cooled to 0 °C, and 2-methylpent-1-en-3-yne **2.189** (241 mg, 1.2 mmol) was added dropwise. The reaction

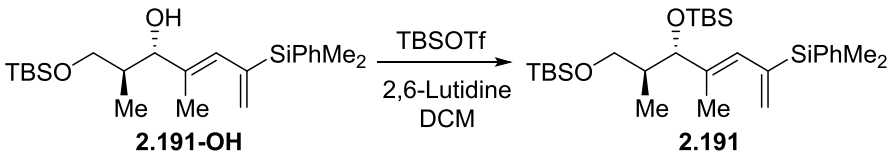
mixture was allowed to stir at 0 °C for 5 min and then stirred at room temperature for 20 min providing a clear solution. Benzaldehyde (10 mg, 0.12 mmol) was added dropwise at room temperature and stirred for another 30 min. The flask was capped and brought out of glove box and cooled to –78 °C. Et_2Zn (0.6 mL, 2.0 M in toluene) was added dropwise and stirred at –78 °C for 30 min. EtZnONf slurry was cannula transferred to the flask at –78 °C in one portion, and the flask was transferred to a cooling bath at –20 °C. A toluene solution (8.0 mL) of the β-silyloxy aldehyde **2.128** (204 mg, 2.0 mmol) was added dropwise. The reaction was allowed to stir at –20 °C overnight. The reaction was quenched with a saturated solution of NH_4Cl (15 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The crude products were concentrated in vacuo and purified by flash chromatography on silica gel (diethyl ether:hexanes 1:10) to afford **2.191-OH** as a colorless oil (160 mg, 49%). R_f = 0.19 (diethyl ether:hexanes=1:20, stain in $KMnO_4$).



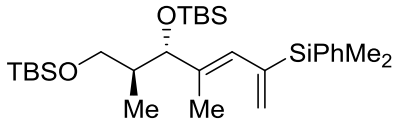
(2*S*,3*S*,*E*)-1-((*tert*-Butyldimethylsilyl)oxy)-6-(dimethyl(phenyl)silyl)-2,4-dimethylhepta-4,6-dien-3-ol (Scheme 2.34, 2.191-OH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.50 (2H, m), 7.35-7.33 (3H, m), 6.00 (1H, s), 5.67 (1H, dd, *J* = 3.5 Hz, 2.0 Hz), 5.56 (1H, t, *J* = 3.5 Hz), 4.00 (1H, d, *J* =2.0 Hz), 3.84 (1H, dd, *J* = 8.5, 2.5 Hz), 3.76 (1H, dd, *J* = 9.5, 4.0 Hz), 3.56 (1H, dd, *J* = 10.0, 8.0 Hz), 1.89-1,84 (1H, m), 1.64 (3H, s), 0.90 (9H, s), 0.65 (3H, d, *J* =7.0 Hz), 0.37 (3H, s), 0.36 (3H, s), 0.08 (3H, s), 0.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 138.0, 137.0, 134.2, 129.4, 129.2, 128.5, 127.9, 84.2, 77.1, 69.0, 37.6, 26.0, 18.3, 13.8, 12.4, −3.0, −3.03, −5.3, −5.4; HRMS-(ESI+) for $C_{23}H_{39}OSi_2$ $[M+H-H_2O]^+$:

calculated: 387.2539, found: 387.2557.

Procedure for tert-Butyldimethylsilyl Protection



A flame-dried round-bottom flask containing a magnetic stir bar, under an atmosphere of nitrogen, was charged with alcohol **2.191-OH** (250.0 mg, 0.62 mmol) in CH_2Cl_2 (3 mL) and 2,6-lutidine (0.14 mL, 1.24 mmol). The reaction flask was cooled to −78 °C, and freshly distilled TBSOTf (0.17 mL, 0.74 mmol) was added dropwise. The reaction was allowed to stir for 1 h until TLC showed full conversion of starting material, and the reaction was quenched with aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (diethyl ether:hexanes=1:20) to afford **2.191** as a clear, colorless oil (263.0 mg, 82%). R_f = 0.77 (diethyl ether:hexanes = 1:20, stain in $KMnO_4$).

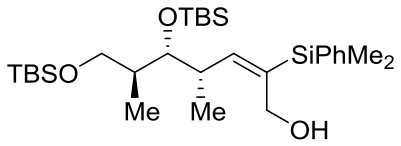


(5*S*,6*S*)-5-((*E*)-4-(Dimethyl(phenyl)silyl)penta-2,4-dien-2-yl)-2,2,3,3,6,9,9,10,10-nonamethyl-4,8-dioxa-3,9-disilaundecane. (Scheme 2.34, 2.191). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52-7.50 (2H, m), 7.35-7.33 (3H, m), 5.81 (1H, s), 5.63 (1H, dd, *J* = 4.0 Hz, 1.5 Hz), 5.54 (1H, dd, *J* = 3.5 Hz, 1.0 Hz), 3.73 (1H, d, *J* = 9.5 Hz), 3.72 (1H, dd, *J* = 10.0 Hz, 7.0 Hz), 3.46 (1H, dd, *J* = 10.0, 7.0 Hz), 1.76-1.70 (1H, m), 0.89 (9H, s), 0.85 (9H, s), 0.70 (3H, d, *J* = 7.0

Hz), 0.37 (3H, s), 0.36 (3H, s), 0.03 (9H, s), −0.01 (3H, s), −0.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ148.0, 138.0, 137.6, 134.2, 129.2, 128.7, 128.4, 128.0, 80.6, 65.3, 40.1, 26.2, 26.1, 18.6, 18.4, 14.1, 12.2, −2.9, −3.0, −4.2, −5.0, −5.1, −5.2.

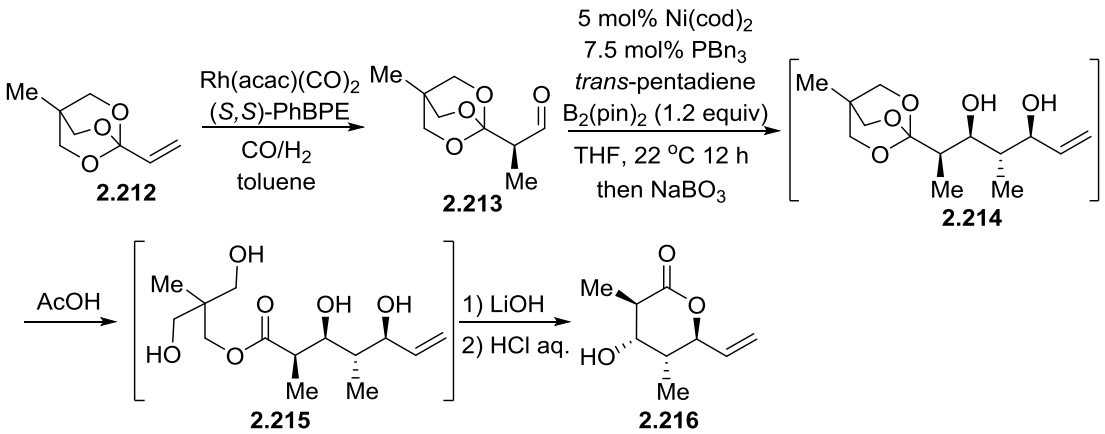
Procedure of Ni-Catalyzed Hydroboration

In dry-box, an oven-dried 6-dram vial containing a magnetic stir bar was charged successively with $Ni(cod)_2$ (1.9 mg, 6.8 μmol), PCy_3 (1.9 mg, 6.8 μmol), THF (0.7 mL), and diene **2.191** (60 mg, 0.12 mmol). The vial was placed in the freezer in glove box for 10 min, and pinacolborane (52 mg, 0.41 mmol, 3.0 equivalents) was added while the vial was cold. The vial was sealed with a polypropylene cap, removed from the dry-box, and allowed warming to 40^{o}C and stir overnight. The reaction mixture cooled to 0 °C and charged with 1.0 mL pH=7 buffer and 0.5 mL 30% *w/w* H_2O_2. The reaction was gradually warmed to room temperature and allowed to stir for 12 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate was added dropwise. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (diethyl ether:hexanes = 1: 10) to afford **2.192** as a clear, colorless oil (32 mg, 50%, >10:1 dr). R_f = 0.41 (hexanes:diethyl ether = 10:1, stain in $KMnO_4$).



(4*S*,5*R*,6*S*,*E*)-5,7-Bis((*tert*-butyldimethylsilyl)oxy)-2-(dimethyl(phenyl)silyl)-4,6-dimethylhept-2-en-1-ol (Scheme 2.34, 2.192). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.52 (2H, m), 7.35-7.33 (3H, m), 5.84 (1H, d, *J* = 9.5 Hz), 4.32 (1H, dd, *J* = 12.5 Hz, 5.0 Hz), 4.21 (1H, dd, *J* = 12.5 Hz, 7.0 Hz), 3.69 (1H, dd, *J* = 10.5 Hz, 6.5 Hz), 3.53 (1H, dd, *J* = 5.0 Hz), 3.40 (1H, dd, *J* = 10.0 Hz, 7.0 Hz), 2.90-2.86 (1H, m), 1.88-1.83 (1H, m), 0.97 (3H, d, *J* = 7.0 Hz), 0.90 (9H, s), 0.89 (9H, s), 0.41 (3H, s), 0.40 (3H, s), 0.06 (3H, s), 0.041 (3H, s), 0.040 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.7, 139.1, 137.8, 134.1, 129.1, 128.0, 77.5, 65.6, 61.0, 41.3, 36.8, 26.3, 26.2, 18.6, 18.5, 17.3, 14.5, −2.2, −2.3, −3.6, −3.7, −5.0, −5.1; IR (neat): 2955 (m), 2929 (m), 2885 (m), 2857 (m), 1472 (w), 1360 (w), 1251 (m), 1087 (m), 1025 (m), 965 (m), 834 (m), 813 (s), 773 (s), 700 (w); HRMS-(ESI+) for $C_{29}H_{57}O_3Si_3$ $[M+H]^+$: calculated: 537.3616, found: 537.3620. $[\alpha]_D^{21} = -18.608$ (*c* = 0.96, $CHCl_3$, *l* = 50 mm).

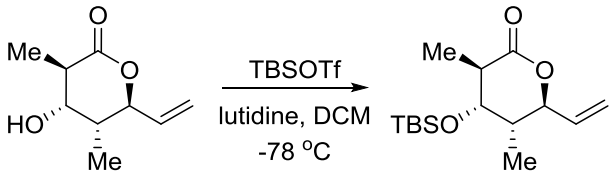
Preparation of δ-Lactone



Vinyl orthoester **2.212** was prepared following literature procedure.[118] Details for asymmetric hydroformylation of **2.212** is included in Chapter 3.

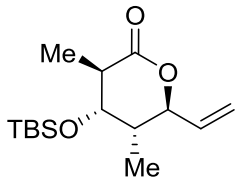
An oven-dried 20 mL scintillation vial, equipped with a magnetic stir-bar, was charged with $Ni(cod)_2$ (13.8 mg, 0.05 mmol), PBn_3 (22.8.mg, 0.075 mmol), and THF (4.0 mL) in a dry box under an argon atmosphere. After stirring for 5 min, the aldehyde **2.213** (186 mg, 1.0 mmol), *trans*-1,3-pentadiene (75 mg, 1.1 mmol) and $B_2(pin)_2$ (303 mg, 1.2 mmol) were added sequentially. The vial was sealed with a polypropylene cap and removed from the dry box. The reaction mixture was allowed to stir at ambient temperature for 14 h. After this time, the mixture was poured into 100 mL round bottom flask with $NaBO_3$ (500 mg, 5 mmol) and water (4.0 mL). The mixture was allowed to stir at ambient temperature for 20 h. The resulting mixture was diluted with water and the two-phase mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was evaporated *in vacuo*. The residue was passed through a pad of Celite with ethylacetate and evaporated *in vacuo*. The crude material was re-dissolved in THF and added several drops of AcOH, and the mixture was allowed to stir at room temperature overnight. The solution was basified with 1.0 M aqueous LiOH and allowed to stir at room temperature for 1h; then the solution was acidified with 3.0 M aqueous HCl until pH=1.0. The reaction mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (ethyl acetate:hexanes = 1: 1) to afford **2.216** contaminated by pinacol. R_f = 0.38 (hexanes:ethyl acetate = 1:1, stain in $KMnO_4$). This mixture was used for next step without further separation.

Procedure for tert-Butyldimethylsilyl Protection



2.216 **2.217**

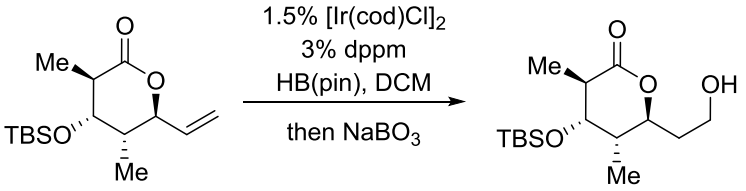
A flame-dried round-bottom flask containing a magnetic stir bar, under an atmosphere of nitrogen, was charged with pinacol contaminated alcohol **2.216** (112 mg with pinacol) in CH_2Cl_2 (3 mL) and 2,6-lutidine (4.0 equivalent to lactone **2.216**). The reaction flask was cooled to −78 °C, and freshly distilled TBSOTf (>2.0 equivalent, depending on the ratio of the lactone **2.216** to pinacol determined by ^{1}H NMR) was added dropwise. The reaction was allowed to stir for 1 h until TLC showed full conversion of starting material, and the reaction was quenched with aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (ethyl acetate:hexanes = 1:10) to afford **2.217** as white solid (124 mg, 44% over two steps). R_f = 0.39 (ethylacetate:hexanes = 1:7, stain in $KMnO_4$).



(3*R*,4*S*,5*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-3,5-dimethyl-6-vinyltetrahydro-2H-pyran-2-one (Scheme 2.36, 2.217). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.81 (1H, ddd, *J* = 17.0 Hz, 10.5 Hz, 7.0 Hz), 5.34 (1H, d, *J* = 17.0 Hz), 5.29 (1H, d, *J* =10.0 Hz), 4.71 (1H, dd, *J* = 7.5 Hz), 3.70 (1H, t, *J* = 2.5 Hz), 2.66 (1H, qd, *J* = 8.0 Hz, 3.5 Hz), 1.92 (1H, qdd, *J* = 7.0 Hz, 7.0 Hz, 2.0 Hz,), 1.28 (3H, d, *J* = 8.0 Hz), 0.99 (3H, d, *J* = 8.0 Hz), 0.90 (9H, s), 0.08 (3H, s), 0.07

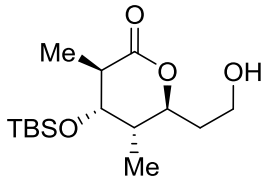
(3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 135.5, 118.9, 82.2, 74.0, 44.0, 34.6, 25.9, 18.2, 16.5, 13.5, −4.3, −4.6; IR (neat): 2978 (w), 2928 (w), 2855 (w), 1725 (s), 1383 (w), 1224 (m), 1104 (m), 1033 (s), 1024 (s), 927 (w), 837 (s), 779 (m); HRMS-(ESI+) for $C_{15}H_{29}O_3Si$ $[M+H]^+$: calculated: 285.1886, found: 285.1890. $[\alpha]_D^{21} = -18.731$ (*c* = 1.0, $CHCl_3$, *l* = 50 mm).

Procedure for Hydroboration of Terminal Olefin[51]



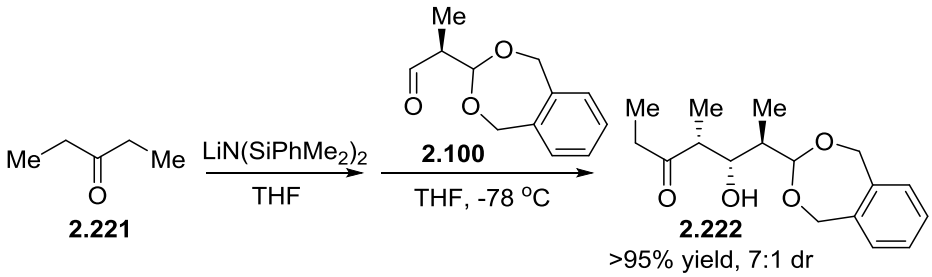
2.217 **2.220**

A flame dried 20-dram vial was charged with $[Ir(cod)Cl]_2$ (1.4 mg, 2.1 μmol) and dppm (1.6 mg, 4.2 μmol), CH_2Cl_2 (0.4 mL), pinacolborane (20 mg, 0.16 mmol), and alkene **2.217** (50 mg, 0.14 mmol) were added successively at room temperature in glove box.. The flask was sealed and brought out of box and was allowed to stir at room temperature overnight. The reaction mixture was concentrated under reduced pressure. THF (1.0 mL), water (1.0 mL) and $NaBO_3$ (70 mg) were added to the residue and was stirred for 10 h at room temperature. The resulting mixture was diluted with water and the two-phase mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the titled compound **2.220** as colorless oil (36 mg, 85%) R_f = 0.44 (ethyl acetate:hexanes=1:1, stain in $KMnO_4$).

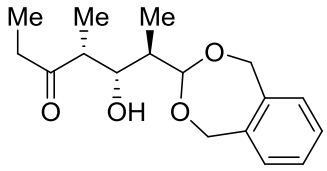


(3*R*,4*S*,5*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-(2-hydroxyethyl)-3,5-dimethyltetrahydro-2H-pyran-2-one (Scheme 2.36, 2.220). All spectrum data are in accordance with literature.[100]

Procedure for Aldol Condensation[120]

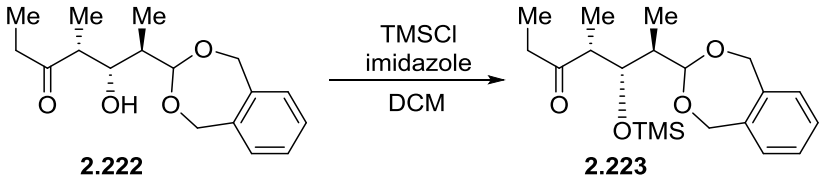


n-BuLi solution (2.5 M in hexane, 0.44 mL, 1.1 mmol) was added dropwise to a dry THF (2.0 mL) solution of $HN(SiPhMe_2)_2$ (314 mg, 1.1 mmol) at 0 °C under N_2 and allowed to stir at that temperature for 30 min. The homogeneous solution was cooled to −78 °C followed by addition of 3-pentanone (104 μL, 1.0 mmol) slowly. The light yellow solution was allowed to stir at −78 °C for 1h, then a dry THF (2.0 mL) solution of aldehyde **2.100** (248 mg, 1.2 mmol) was added slowly *via* syringe along the flask inner wall. After stirring at −78 °C for 2h, the reaction was quenched with NH_4Cl aqueous solution. The resulting mixture was diluted with water and the two-phase mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The residue was purified by silica gel chromatography to afford the titled compound **2.222** as colorless oil (300 mg, >95% yield). R_f = 0.34 (ethyl acetate:hexanes=1:4, stain in $KMnO_4$).



(4*R*,5*S*,6*R*)-6-(1,5-Dihydrobenzo[*e*][1,3]dioxepin-3-yl)-5-hydroxy-4-methylheptan-3-one (Scheme 2.37, 2.222). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.18 (4H, m), 5.07 (1H, d, *J* = 3.5 Hz), 4.97 (1H, d, *J* = 14.0 Hz), 4.92 (1H, d, *J* = 14.0 Hz), 4.851 (1H, d, *J* =14.0 Hz), 4.848 (1H, d, *J* = 14.0 Hz), 4.01 (1H, ddd, *J* = 9.0 Hz, 3.0 Hz, 3.0 Hz), 3.47 (1H, d, *J* = 2.5 Hz), 2.65 (1H, qd, *J* = 7.0, 3.0 Hz), 2.54 (2H, q, *J* = 7.0 Hz), 1.98-1.94 (1H, m), 1.12 (3H, d, *J* = 7.0 Hz), 1.05 (3H, t, *J* =7.5 Hz), 0.94 (3H, d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 215.6, 139.6, 139.5, 128.0, 127.9, 111.7, 73.9, 73.6, 48.0, 40.9, 34.4, 11.6, 9.3, 7.9; IR (neat): 3502 (b), 2976 (m), 2904 (m), 2850 (w), 1707 (s), 1456 (m), 1375 (m), 1301 (w), 1261 (w), 1106 (s), 1029 (s), 975 (m), 921 (w), 773 (w), 739 (w); HRMS-(ESI+) for $C_{17}H_{25}O_4$ $[M+H]^+$: calculated: 293.1753, found: 293.1743. $[\alpha]_D^{21}$ = −11.474 (*c* = 1.0, $CHCl_3$, *l* = 50 mm).

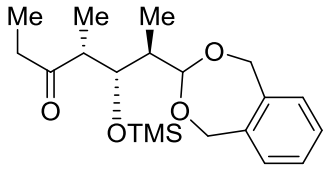
Procedure for TMS-Protection



2.222 **2.223**

TMSCl (128 μL, 1.02 mmol) was added dropwise to a dry CH_2Cl_2 solution of alcohol **2.222** (270 mg, 0.92 mmol) and imidazole (125 mg, 1.84 mmol) at room temperature. Once TLC showed full conversion of starting material (usually < 20 min), the reaction was quenched with $NaHCO_3$ aqueous solution. The resulting mixture was diluted with water and the two-phase mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the

solvent was evaporated *in vacuo*. The residue was purified by triethylamine neutralized silica gel chromatography to afford the titled compound **2.223** as colorless oil (289 mg, 86% yield). R_f = 0.50 (ethyl acetate:hexanes=1:10, stain in $KMnO_4$).



(4*R*,5*S*,6*R*)-6-(1,5-Dihydrobenzo[e][1,3]dioxepin-3-yl)-4-methyl-5-((trimethylsilyl)oxy)heptan-3-one (Scheme 2.37, 2.223). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.18 (4H, m), 4.93 (1H, d, *J* = 4.5 Hz), 4.84-4.81 (4H, m), 4.12 (1H, dd, *J* = 6.5 Hz, 5.0 Hz), 2.97 (1H, qd, *J* = 7.0 Hz, 5.0 Hz), 2.51 (2H, dq, *J* = 13.5 Hz, 7.5 Hz), 1.93 (1H, qdd, *J* = 7.0 Hz, 7.0 Hz, 5.0 Hz), 1.09 (3H, d, *J* = 7.0 Hz), 1.03 (3H, t, *J* = 7.0 Hz), 0.93 (3H, d, *J* = 7.5 Hz), 0.14 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.1, 139.9, 139.7, 127.8, 127.7, 109.4, 74.8, 73.3, 72.7, 49.2, 42.8, 34.9, 12.1, 11.7, 7.9, 0.93; IR (neat): 2955 (m), 2891 (w), 2842 (w), 1712 (s), 1455 (w), 1374 (w), 1250 (s), 1121 (s), 1099 (s), 1043 (s), 973 (w), 890 (m), 950 (m), 840 (s), 740 (m); HRMS-(ESI+) for $C_{20}H_{33}O_4Si$ $[M+H]^+$: calculated: 365.2148, found: 365.2154. $[\alpha]_D^{21} = -39.099$ (*c* = 0.52, $CHCl_3$, *l* = 50 mm).

2.7. Unpublished Spectrums

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Me
Me
Me
Me
N
Bn
SO2Mes
10
9
8
7
6
5
4
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Me
Me
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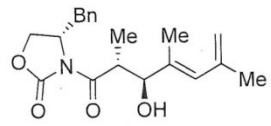

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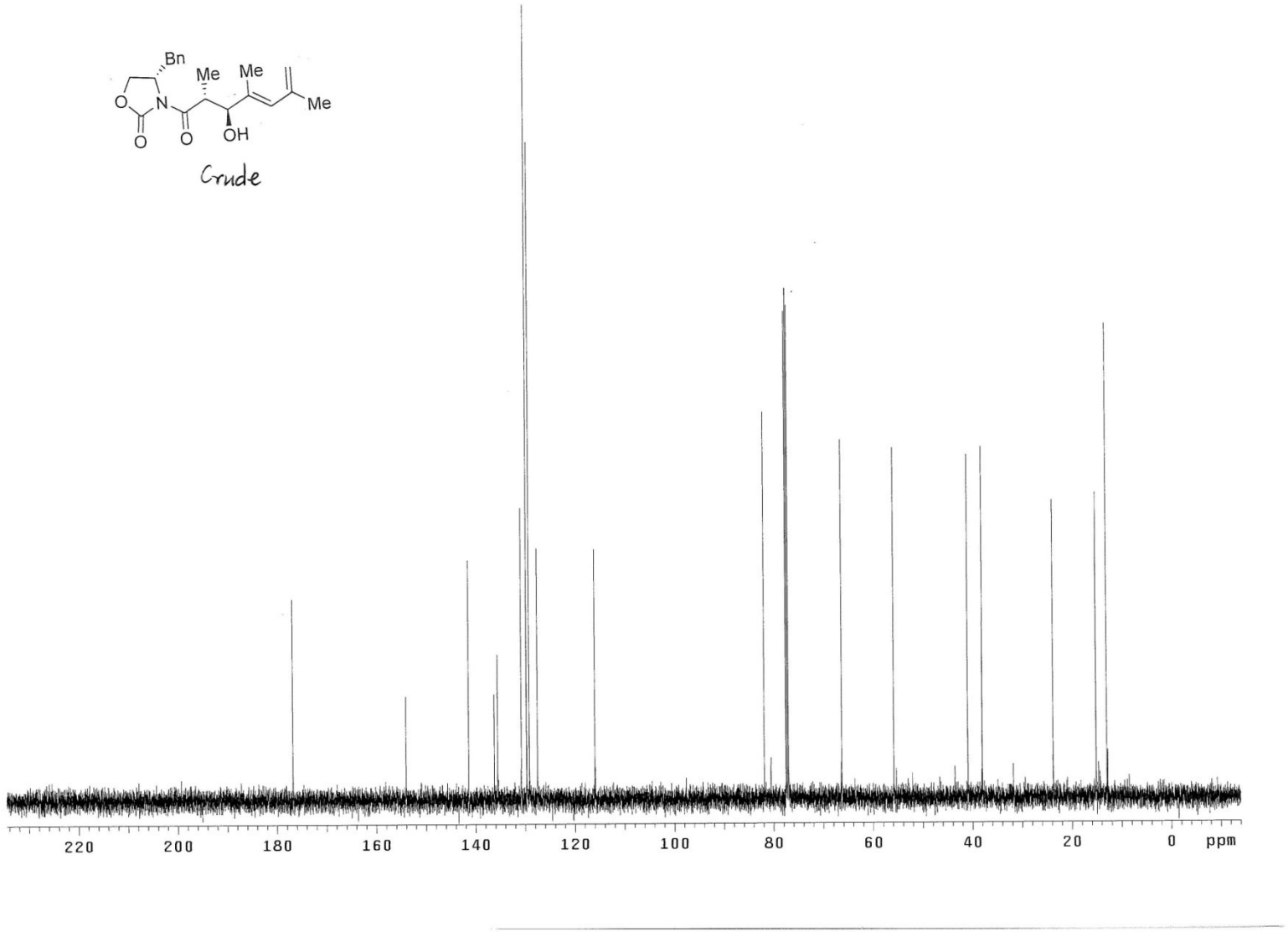
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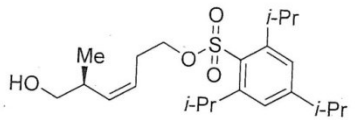
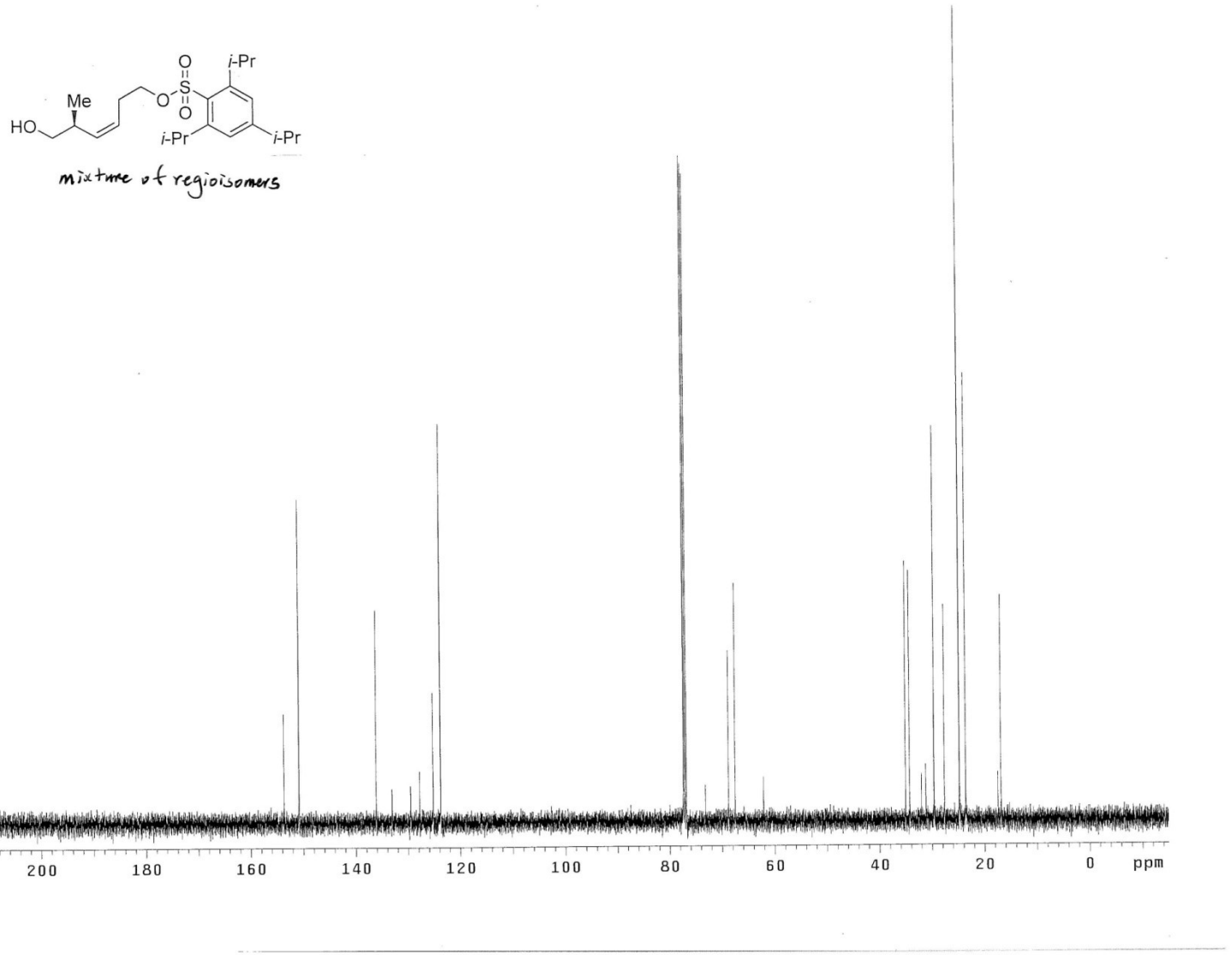


mixture of regioisomers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i-Pr
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mixture of regioisomers
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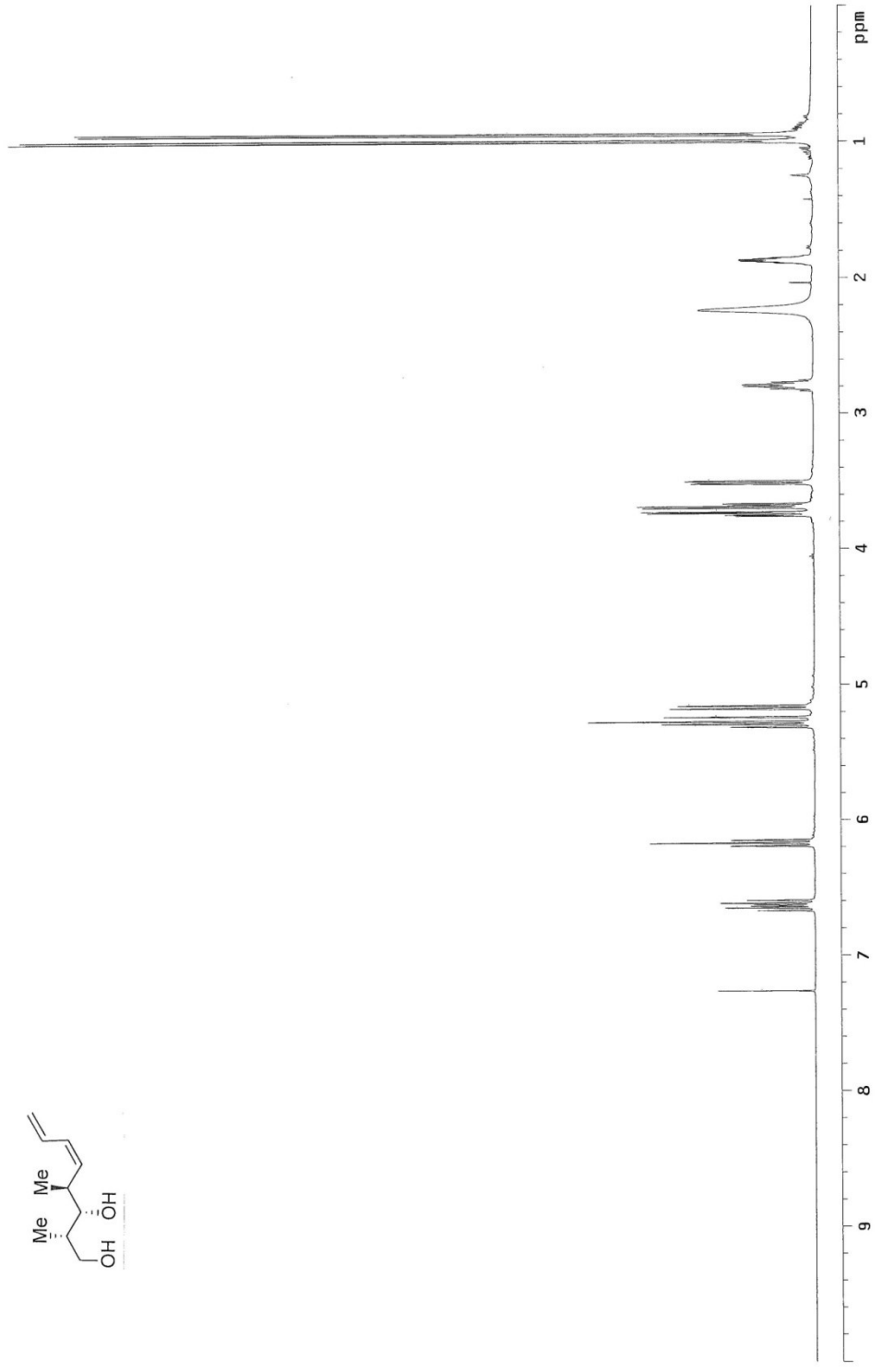
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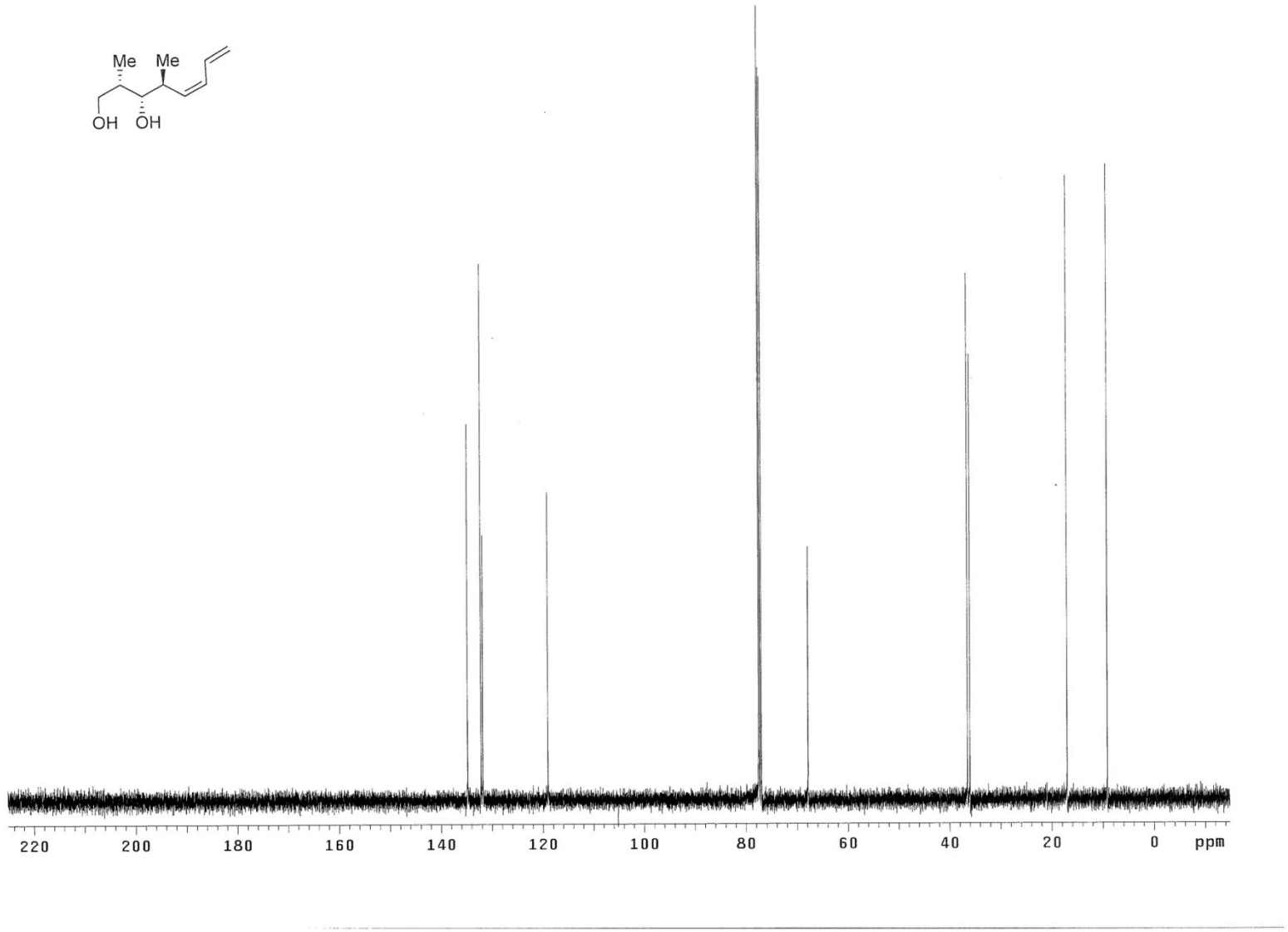
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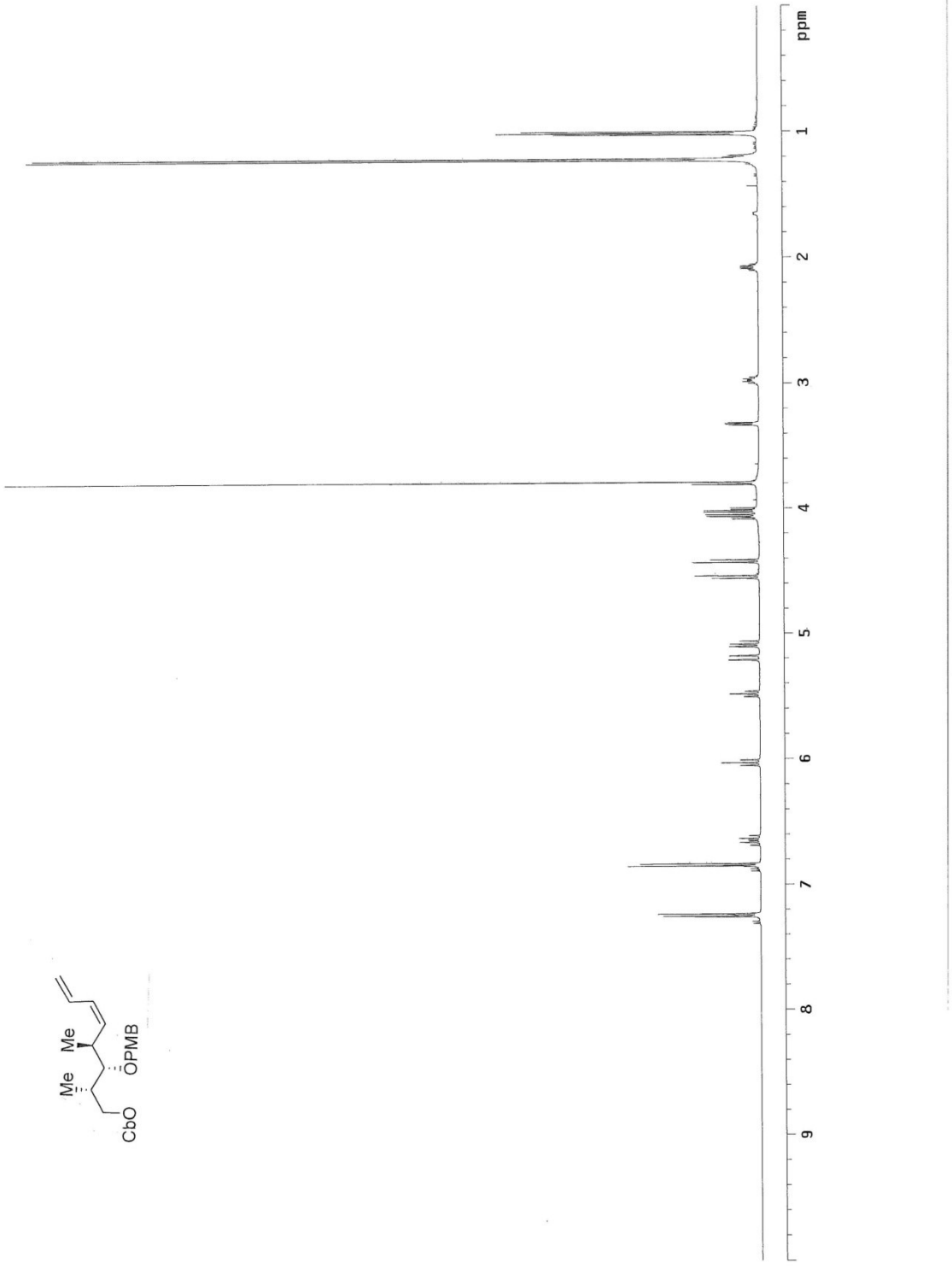
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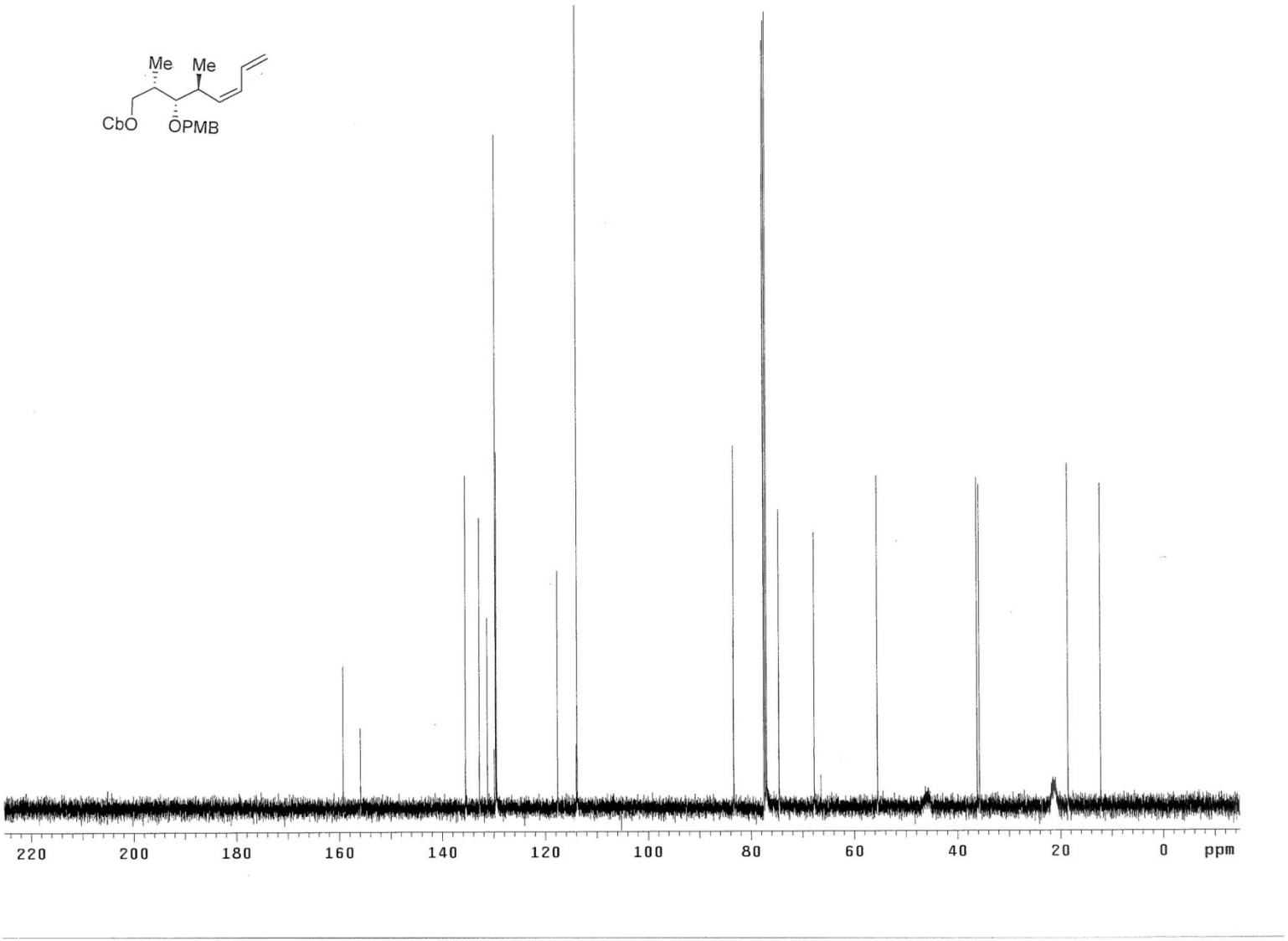
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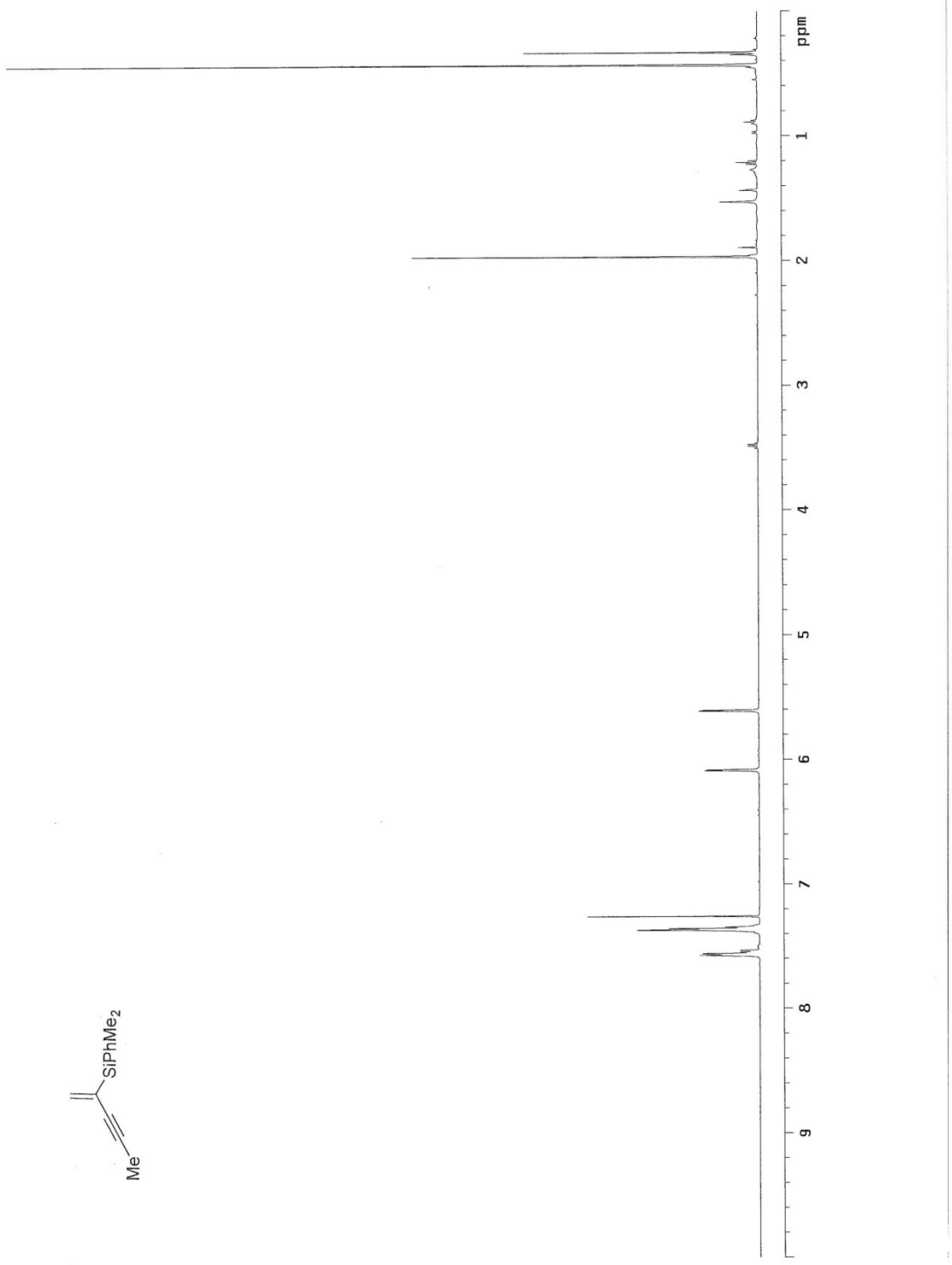
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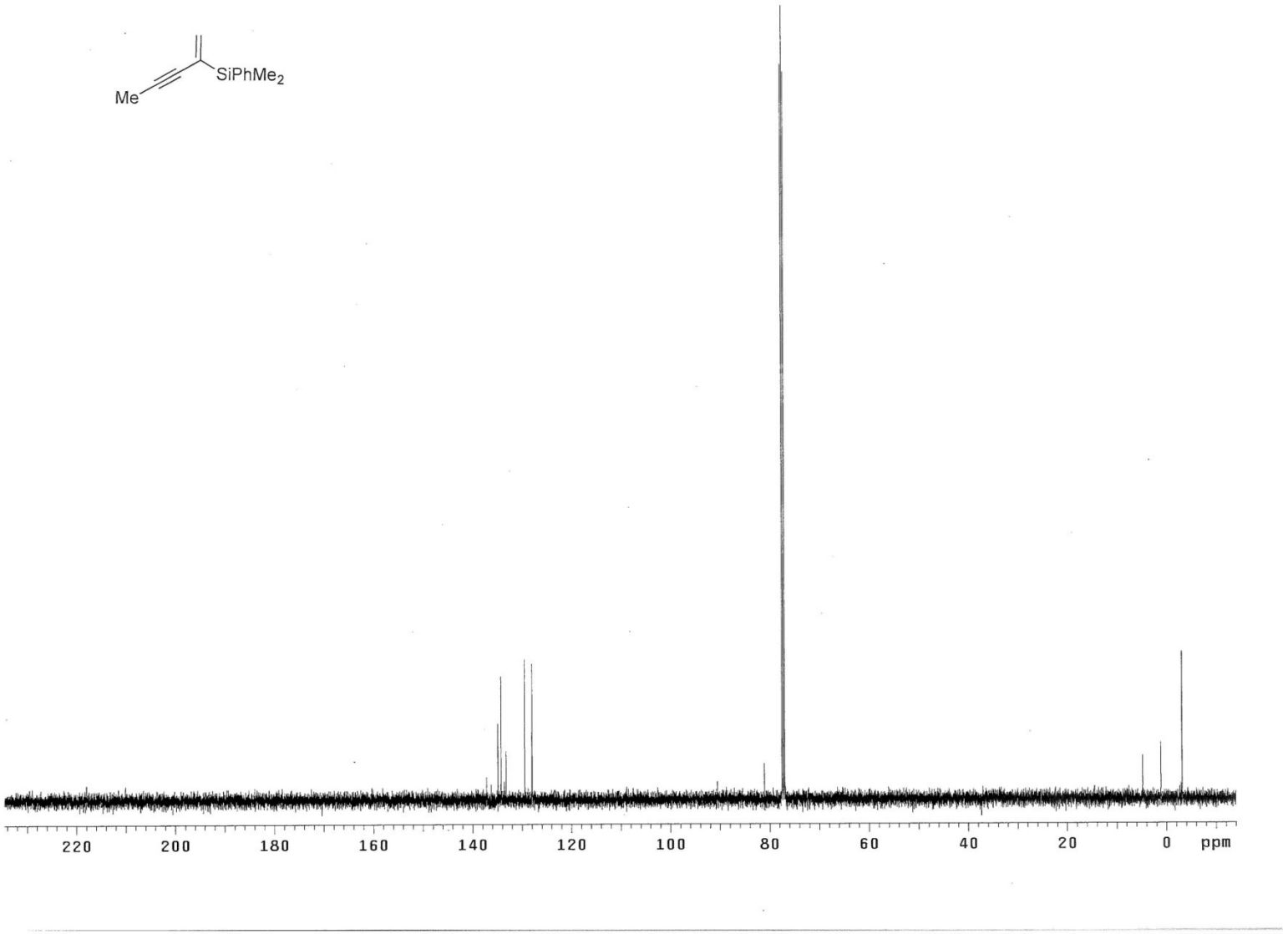
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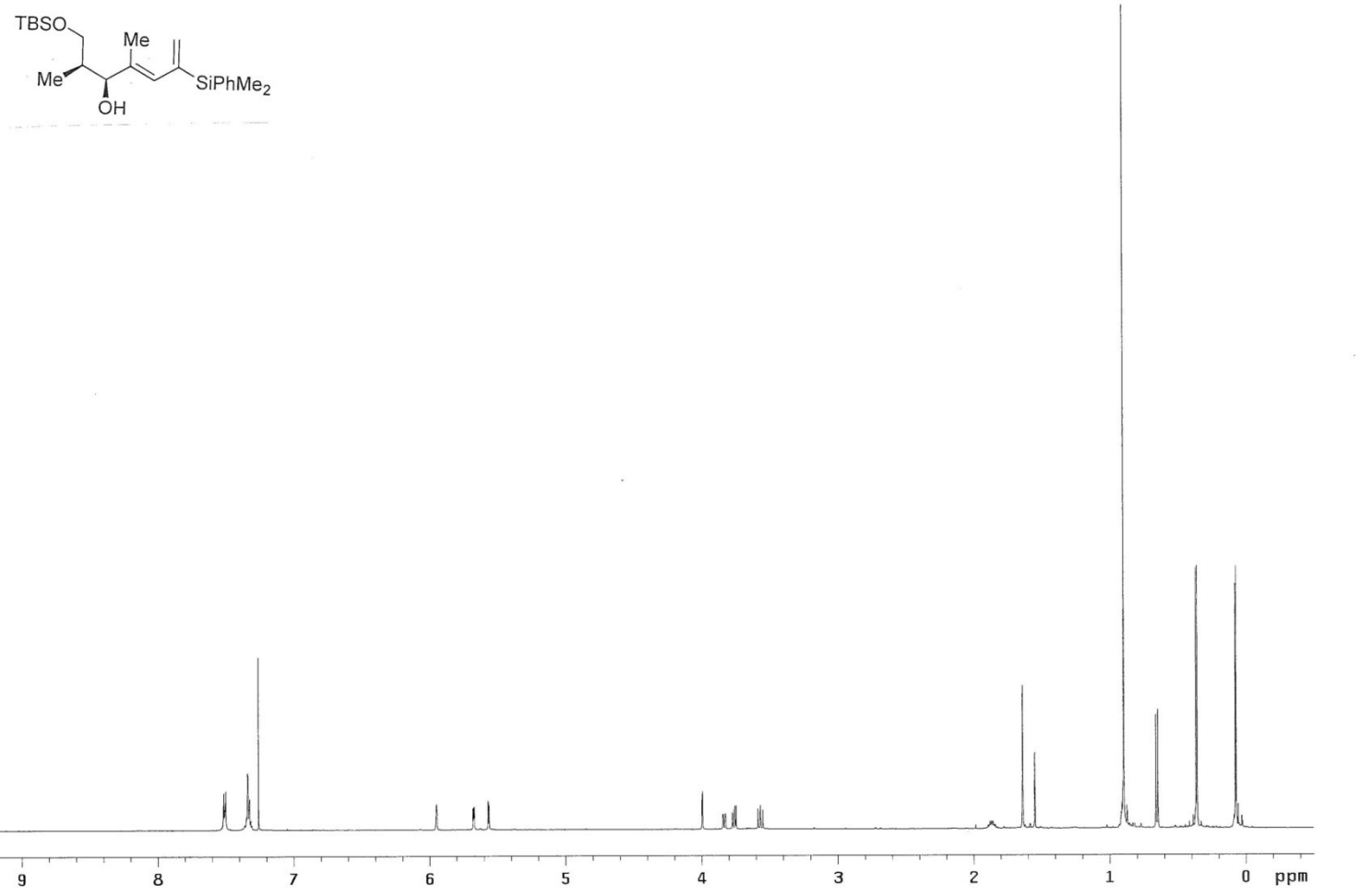
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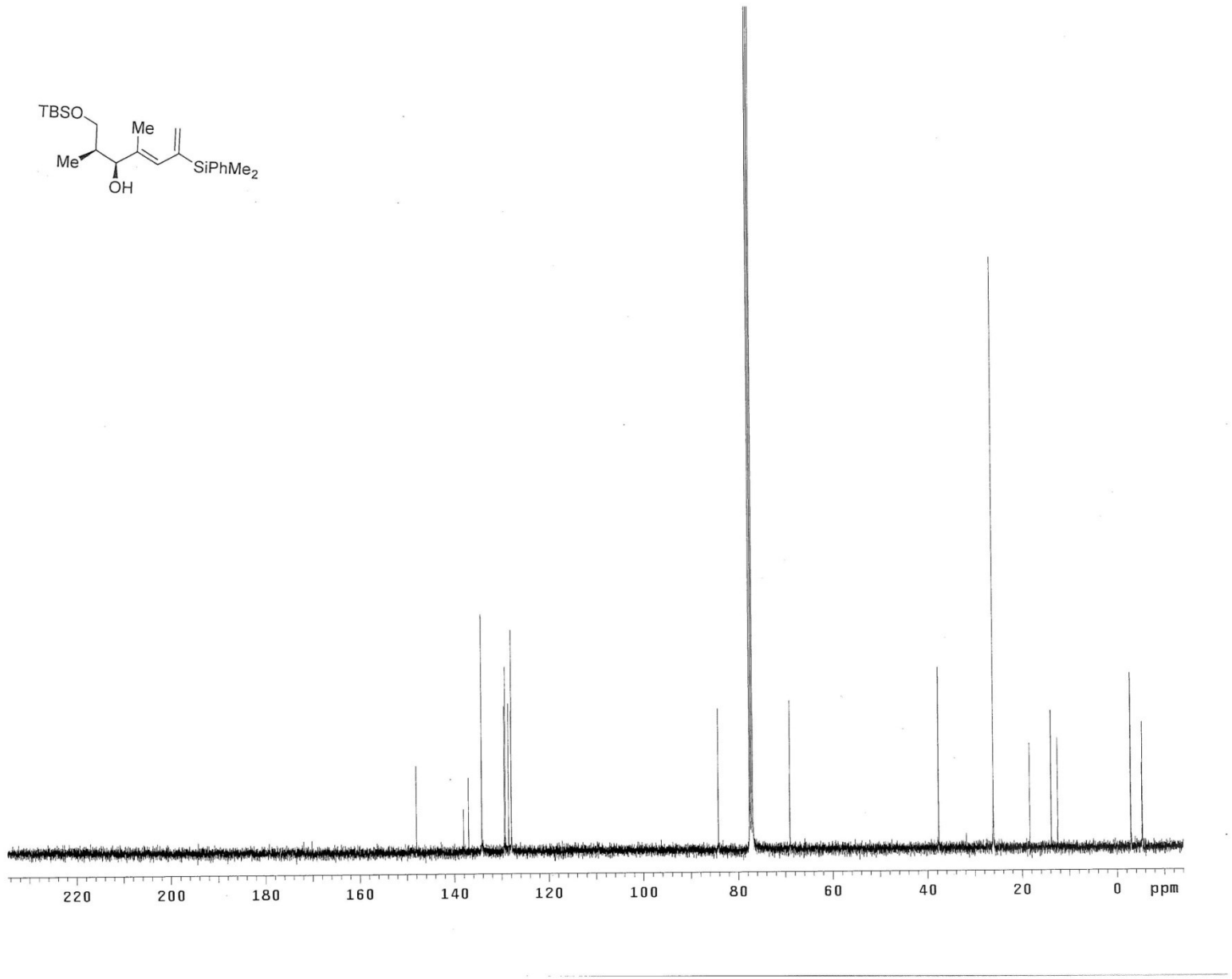
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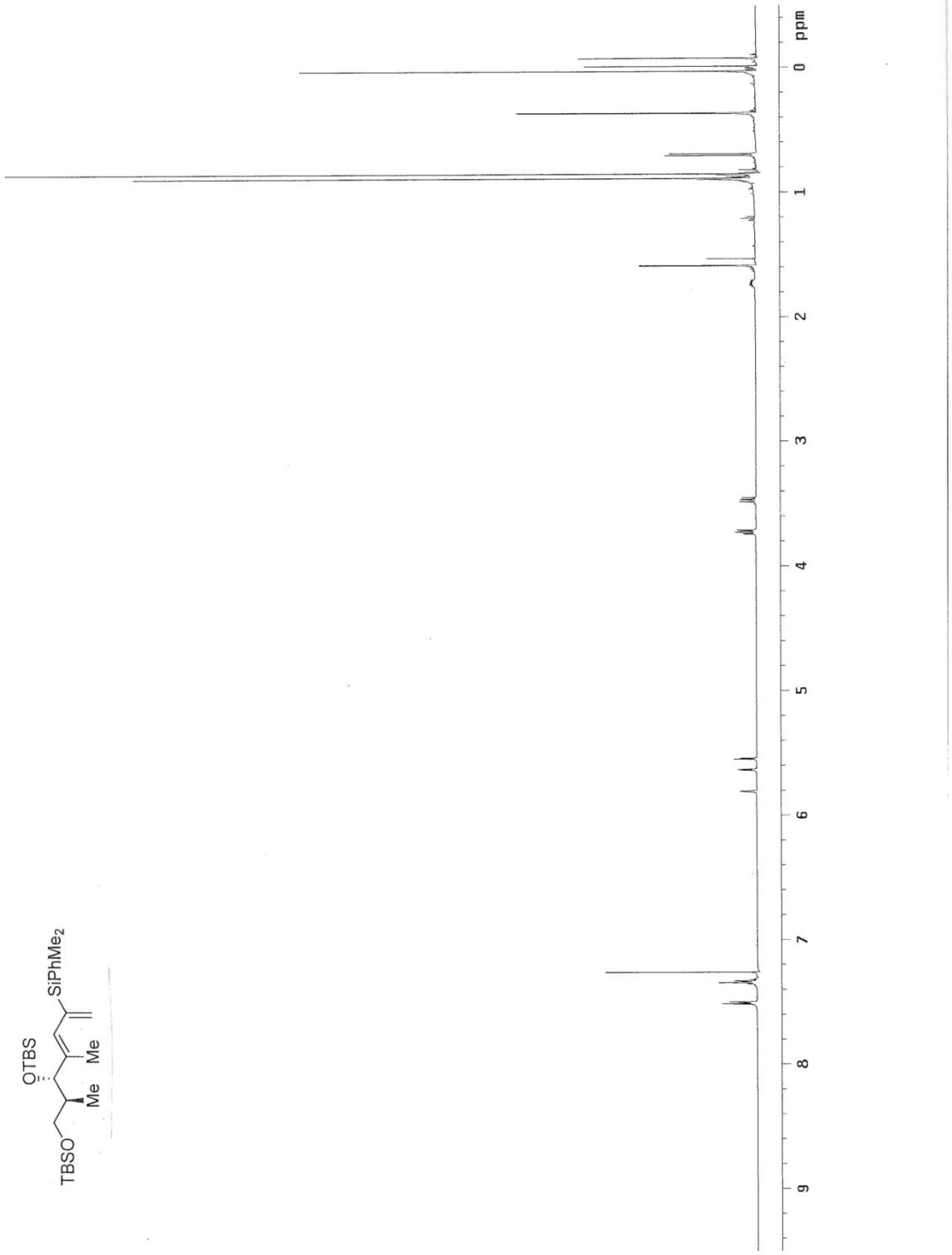
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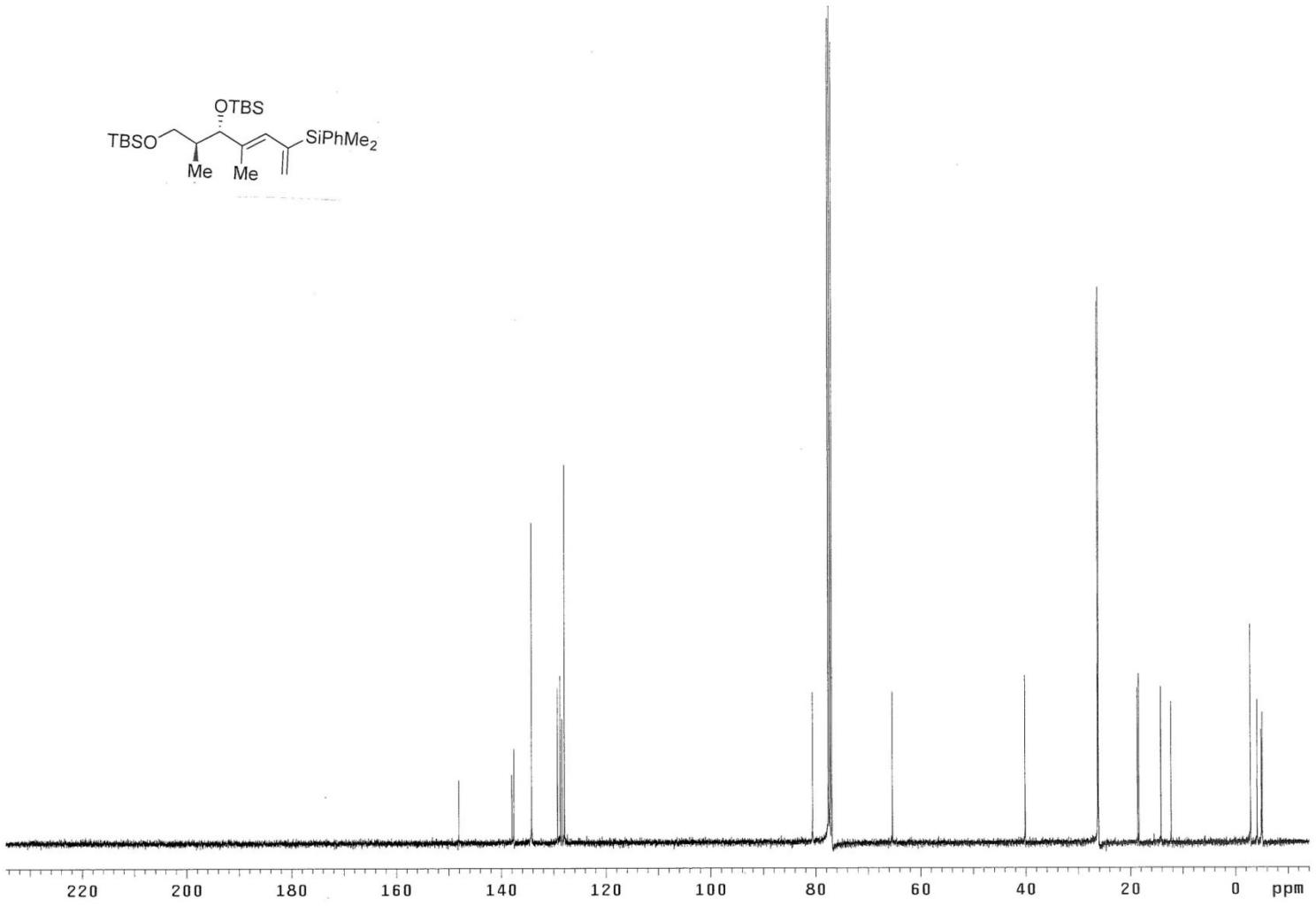
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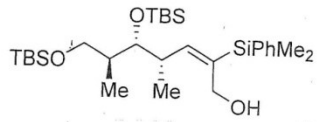
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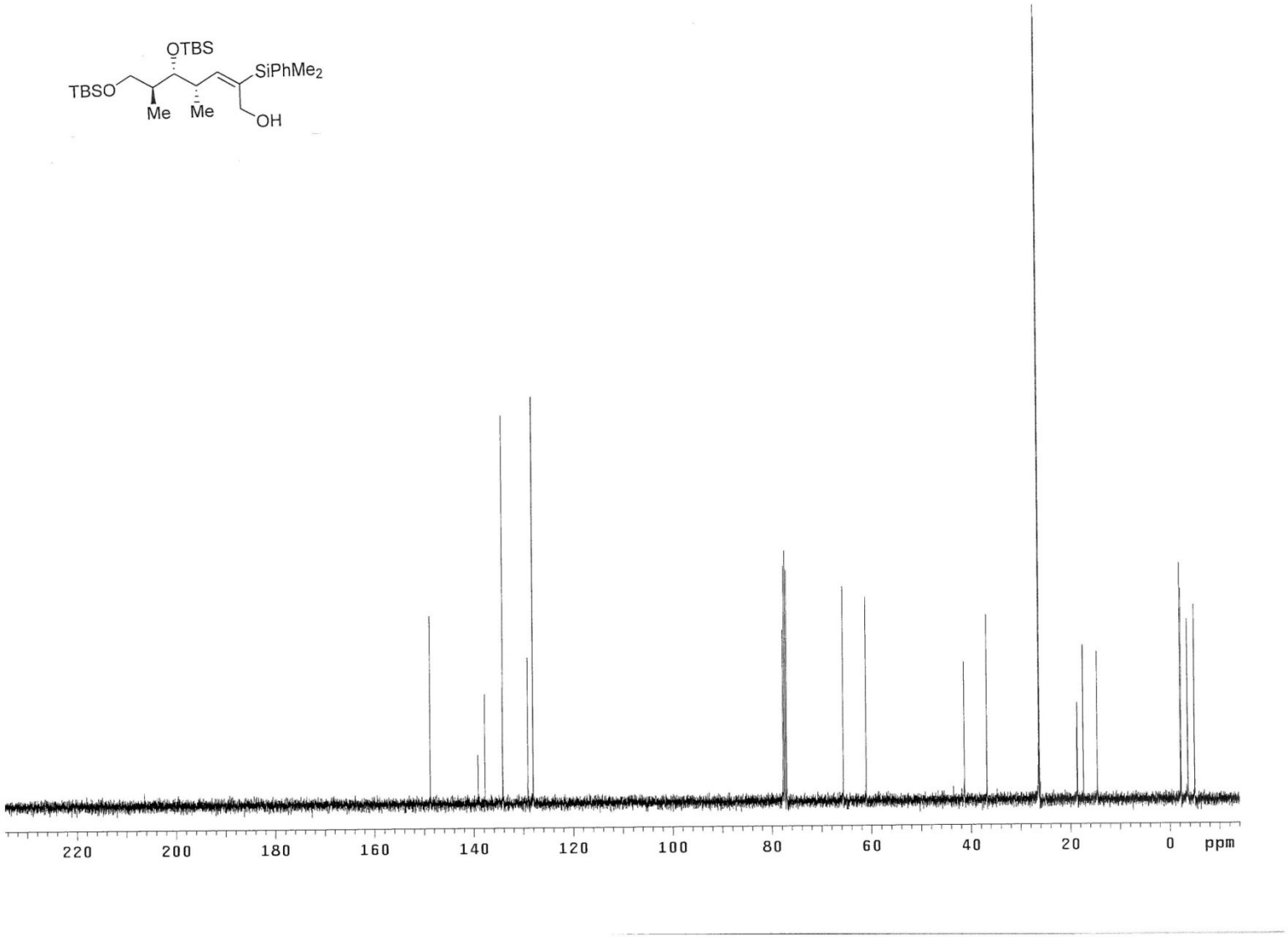
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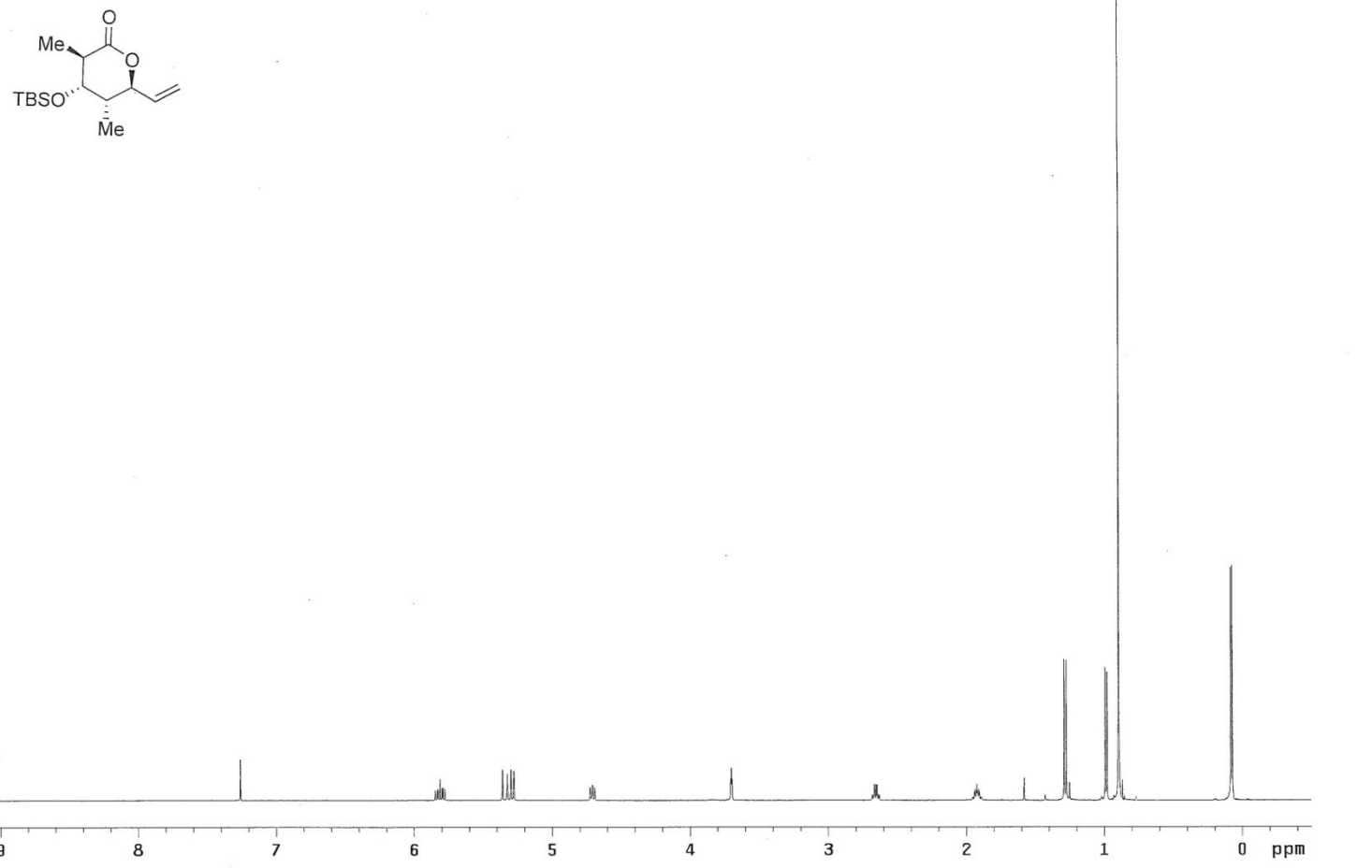
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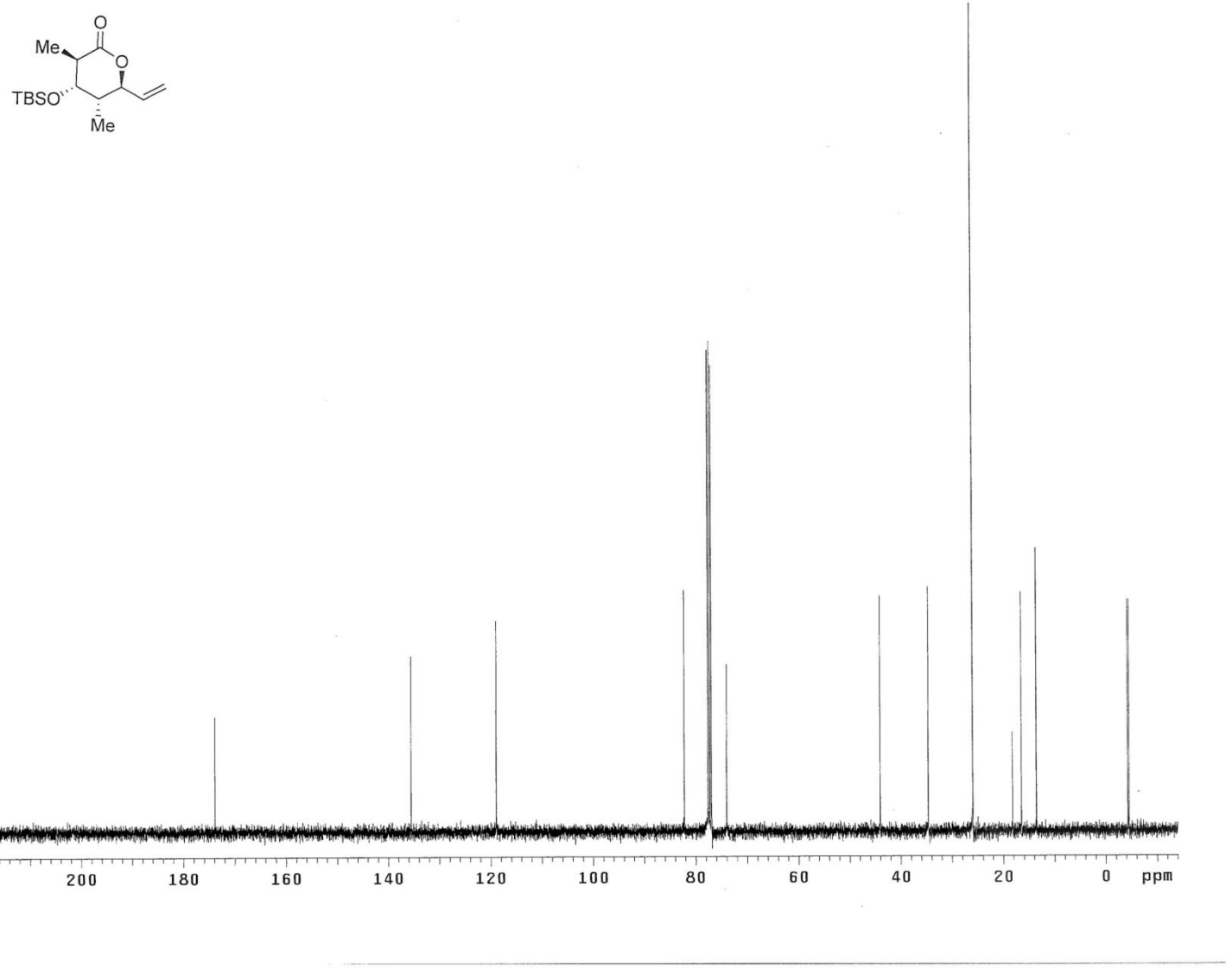
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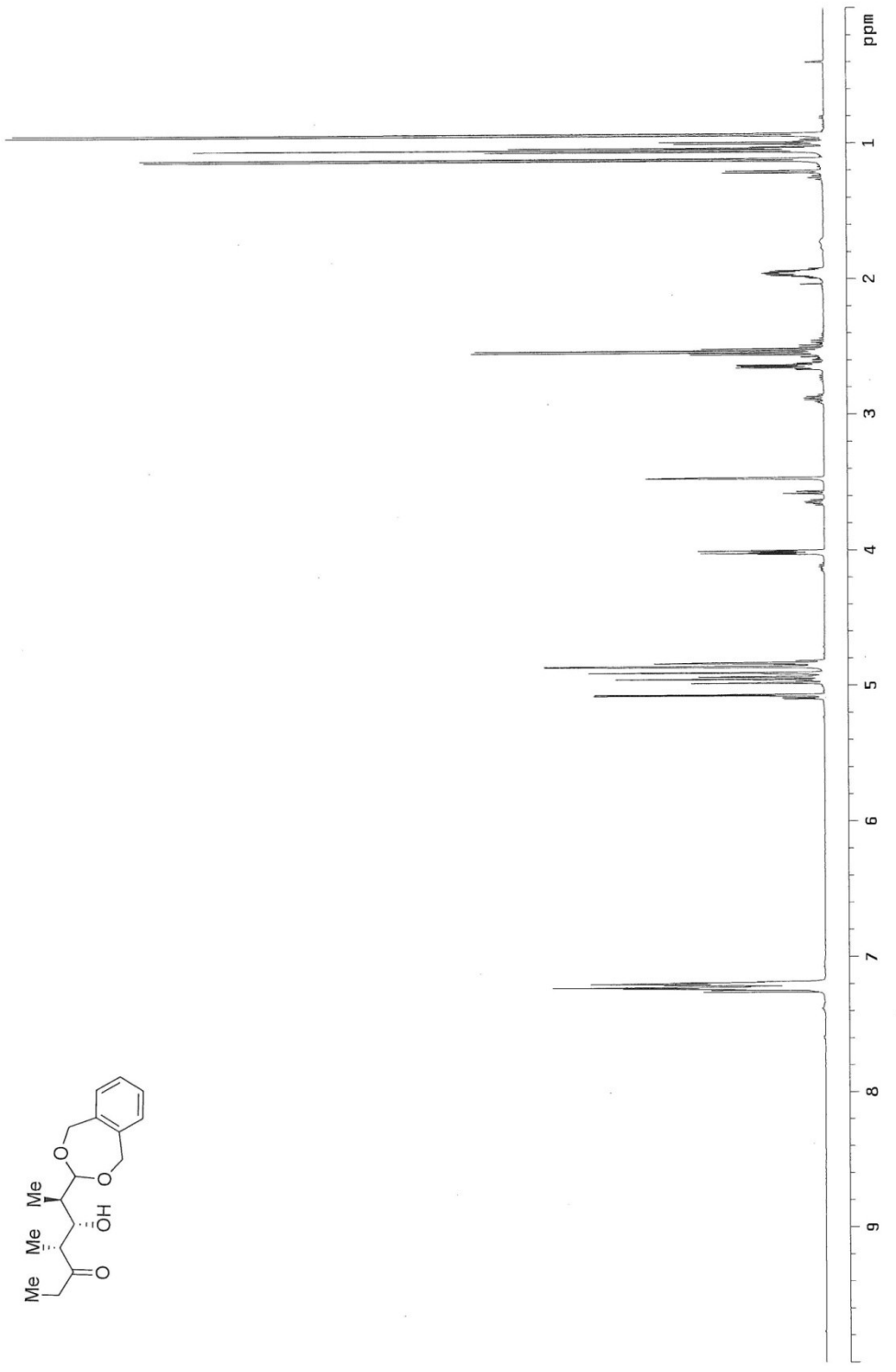
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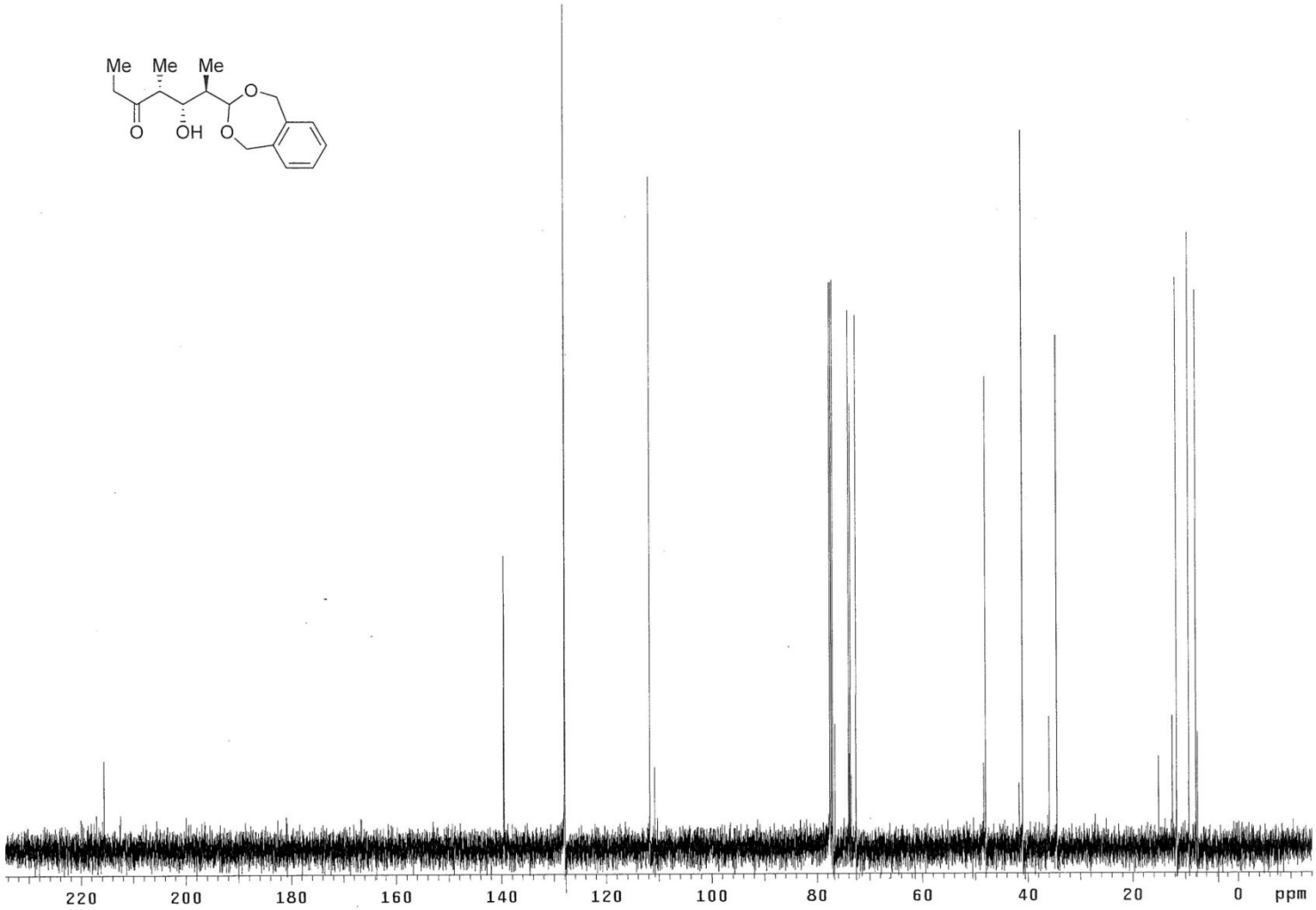
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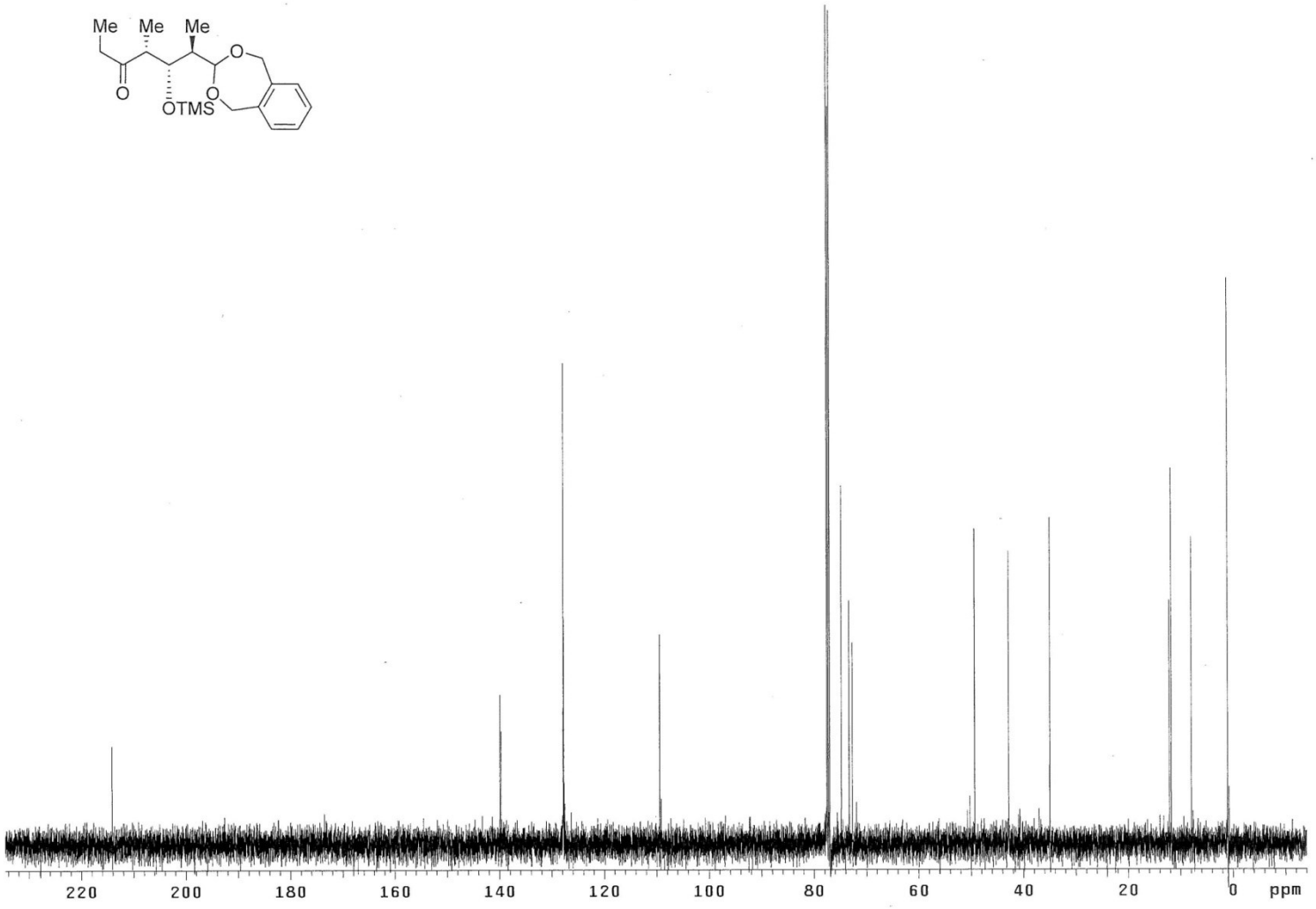
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60
40
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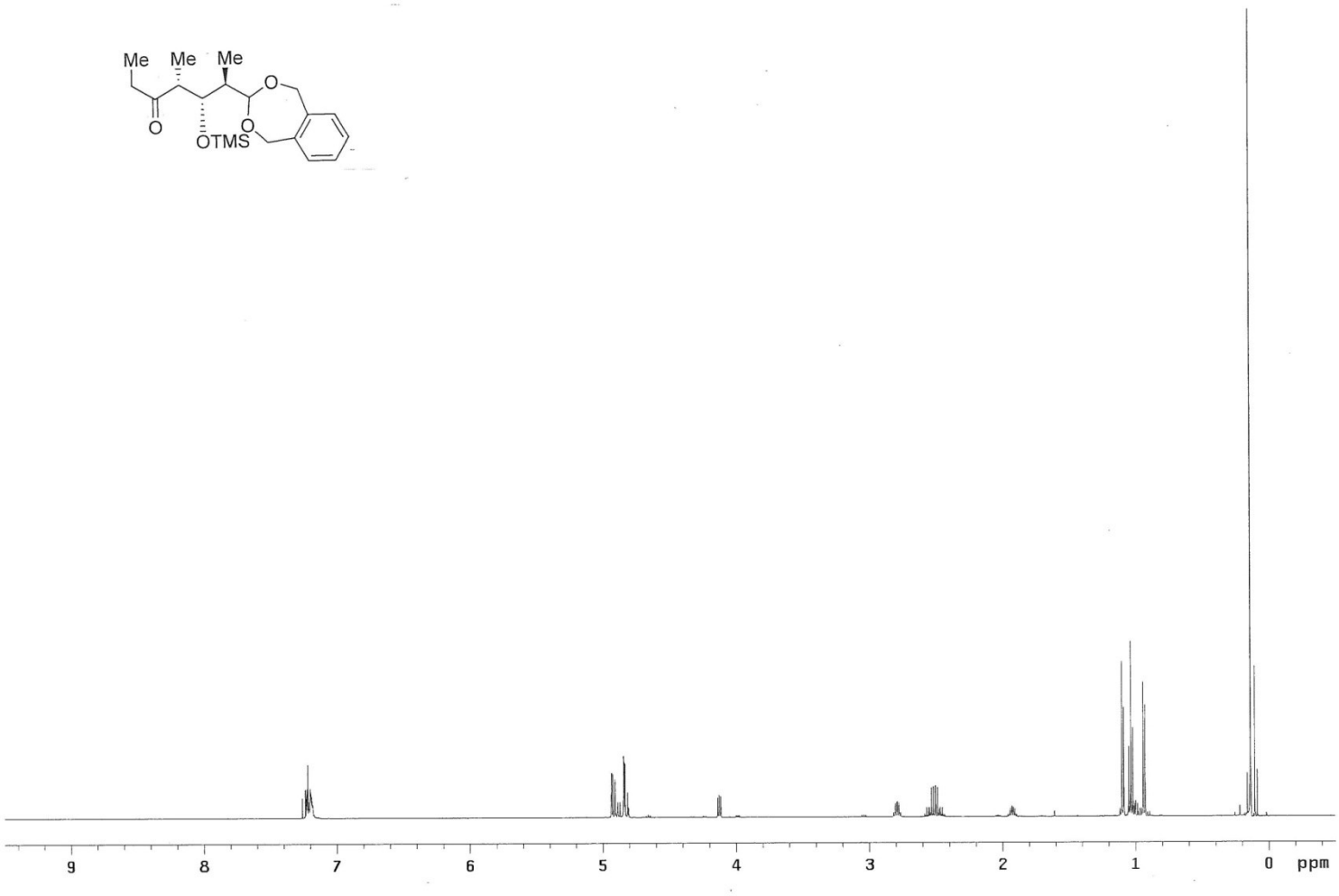
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Chapter 3

Asymmetric Hydroformylation of Terminal Olefins with Readily Available Ligand[1]

3.1 Introduction

Discovered by Roelen in 1938,[2] rhodium catalyzed hydroformylation of alkenes has become one of the largest industrial processes producing billions of pounds of achiral aldehydes per year. It is preeminent in catalytic manufacturing is due to its perfect atom economy, fast reaction rates, high turn-over numbers, and mild conditions as well as the versatility of aldehyde products.[3] Hydroformylation of a terminal alkene gives two distinct products, a linear achiral aldehyde **3.1** and a branched constitutional isomer **3.2** (Scheme 3.1). Though many advances have been made to produce the linear aldehyde **3.1**, selective construction of branched aldehyde **3.2** still remains underdeveloped, especially in a catalytic asymmetric fashion. The branched, optically pure aldehydes **3.2** are important building blocks for organic syntheses, and their one-step syntheses *via* the asymmetric hydroformylation (AHF) from inexpensive feedstocks (olefin, syngas) would be extremely attractive and valuable. Thus, it is of great importance to solve the challenges in controlling regio- and enantioselectivity of hydroformylation of simple alkenes.

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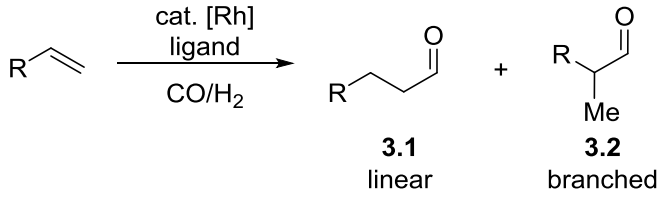
[1] Yu, Z.; Eno, M. S.; Annis, H. A.; Morken, J. P. manuscript in preparation.
[2] Roelen, O. *Chem. Abstr.* **1944**, *38*, 550.
[3] *Rhodium Catalyzed Hydroformylation*; Claver, C., van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2000.

Scheme 3.1. Hydroformylation of Terminal Olefins

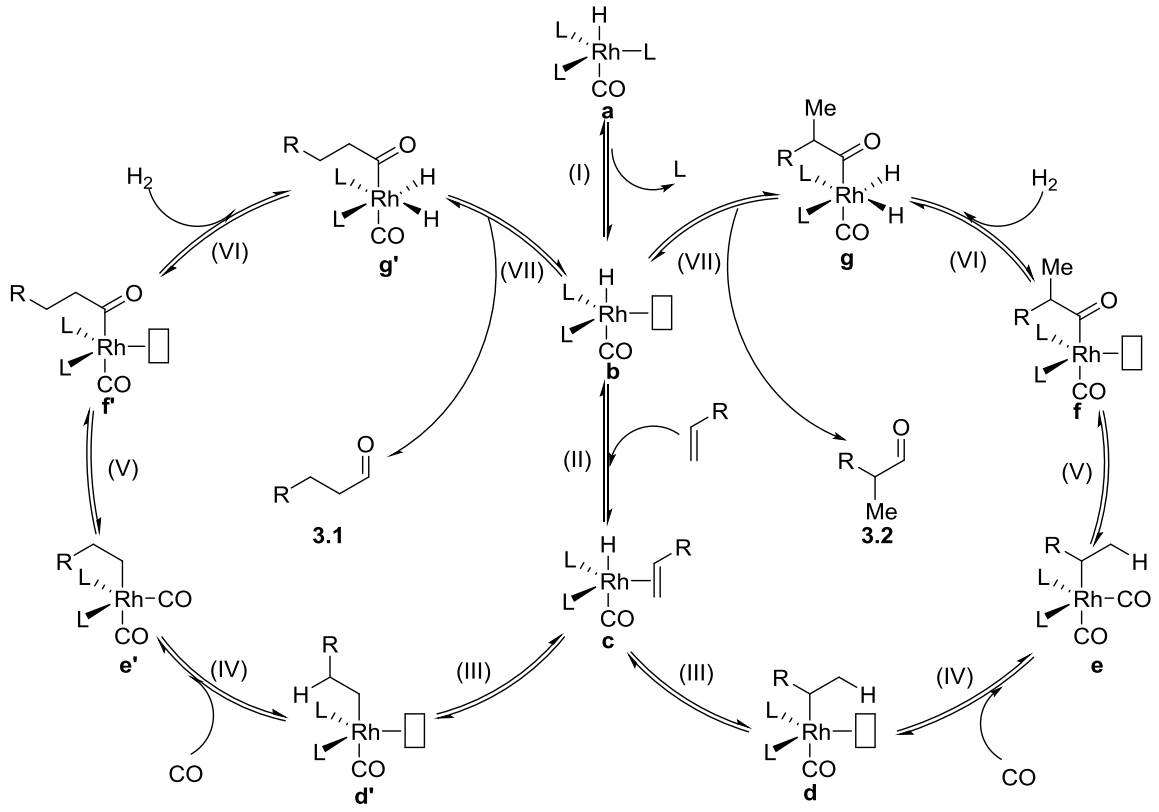


3.2 Background

As mentioned above, it is important to control regioselectivity for asymmetric hydroformylation, because undesired linear isomer could be regarded as an "impurity" which has very similar chemical and physical properties making purification a challenging task. The widely accepted *dissociative mechanism* can explain the origin of regioselectivity (Figure 3.1).[4] Coordination of the alkene to open site of complex **b** furnishes hydrido olefin complex **c**. The subsequent migratory insertion of Rh-H bond (III) can occur in two ways providing isomeric complexes **d** and **d'**. This is the regioselectivity determining step, having more stable complex **d** results higher ratio for branched aldehyde **3.2**, and *vice versa*. Subsequent CO coordination (IV) and migratory insertion (V) give acyl complexed **f** and **f'**. Oxidative addition of molecular hydrogen (VI) followed by reductive elimination (VII) regenerates the active rhodium catalyst **b** after liberating aldehyde **3.2** and **3.1**. Thus, the regioselectivity is determined, in part, by intrinsic substrate preference to avoid steric interactions and create a more stable intermediate **d** or **d'**. Alkenes with different substitution patterns will be discussed under different context.

[4] (a) Torrent, M.; Solà, M.; Frenking, G. *Chem. Rev.* **2000**, *100*, 439. (b) Nozaki, K.; Ojima, I. In *Catalytic Asymmetric Synthesis;* 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000, p 429.

Figure 3.1. Rhodium-Catalyzed Hydroformylation of Alkenes



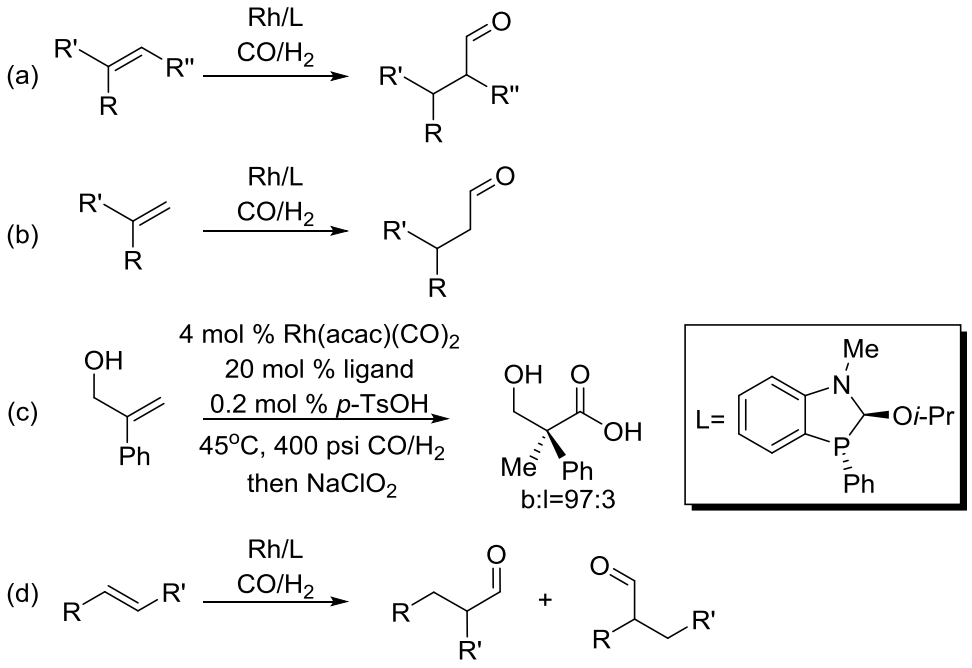
3.2.1. Hydroformylation of 1,1-Disubstituted and Trisubstituted Alkenes

1,1-Disubstituted and trisubstituted alkenes generally only provide one regioisomeric product based on Keulemans' rule:[5] the formyl group is attached such to avoid the formation of a quaternary carbon (Scheme 3.2a and Scheme 3.2b). In other words, only complex **d'** would be formed to avoid severe steric interacetion (Figure 3.1). However, a scaffold ligand, pioneered by Tan and co-workers, completely turned over such intrinsic preference, and successfully built all carbon-quaternary center *via* hydrofromylation of 1,1-disubstituted alkenes (Scheme 3.2c). [6] Furthermore, nonsymmetrical 1,2-disubstituted alkenes are also challenging substrates, and their

[5] Keulemans, A. I. M.; Kwantes, A.; van Bavel, T. *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 298.
[6] (a) Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc*. **2010**, *132*, 11841. (b) Tan, K. L.; Sun, X.; Worthy, A. D. *Synlett*, **2012**, *23*, 321.

regioselective hydroformylation remains unsolved (Scheme 3.2d). While the use of directing groups to control hydroformylation regioselectivity is a proven strategy,[7] these examples will not be covered here.

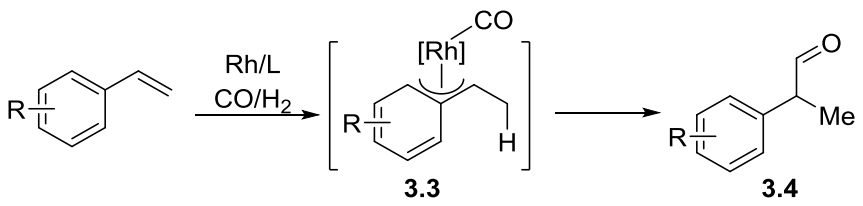
Scheme 3.2. Hydroformylation of 1,1-Disubstituted and Trisubstituted Alkenes



3.2.2. Hydroformylation of Styrene Derivatives and Vinyl Ethers

Styrene derivatives preferentially form the branched regioisomer **3.4** due to the formation of stable π-benzyl intermediate **3.3**[8] representing compex **d** (Figure 3.1) after alkene hydrometalation (III).

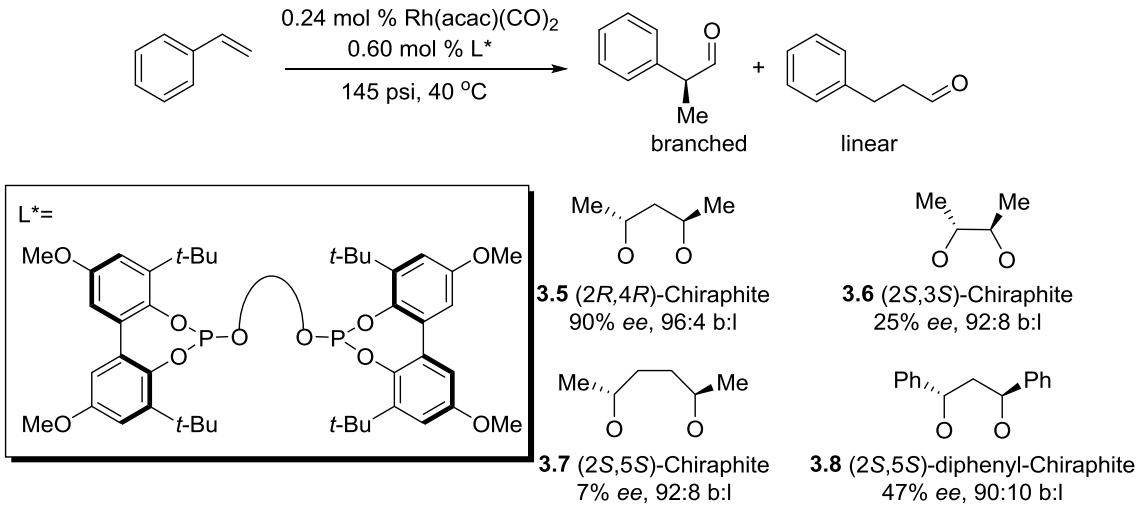
Scheme 3.3. Hydroformylation of Styrene Derivatives



[7] Rousseau, G.; Breit, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 2450.
[8] (a) Tanaka, M.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. *Bull. Chem. Soc. Jpn* **1974**, *74,* 1698. (b) O'Connor, C. *J. Inorg. Nucl. Chem.* **1970**, *32*, 2299.

Thus, styrene derivatives are the most studied substrates for asymmetric hydroformylation due to their inherent preference for branched isomer. The initial success of rhodium catalyzed asymmetric hydroformylation of styrene was from Union Carbide using a bis-phosphite ligand, (2*R*, 4*R*)-chiraphite **3.5**.[9] Good enantioselectivity (90% *e.e.*) was obtained with this ligand but only when the reaction was carried out near room temperature with a 2.5:1 ligand/metal ratio. Further studies from van Leeuwen and co-workers demonstrated that different length of the diolate bridge and substitution on the bridge (Scheme 3.4, ligand **3.6**, **3.7** and **3.8**) caused significant decrease in enantioselectivity.[10]

Scheme 3.4. Asymmetric Hydroformylation of Styrene with Chiraphite Ligands



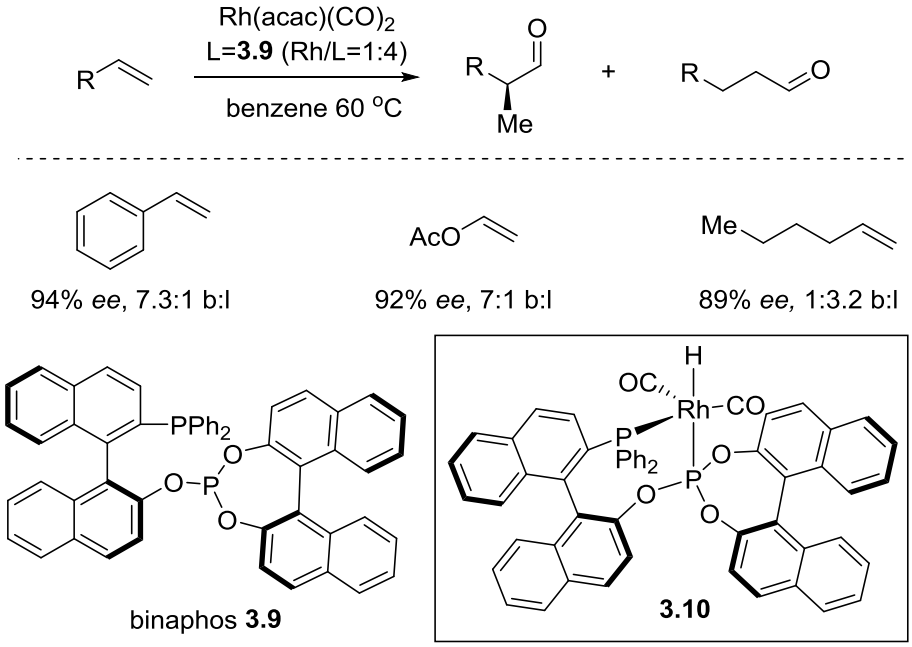
The major break-through for rhodium-catalyzed asymmetric hydroformylation was made using a phosphine-phosphite ligand, binaphos **3.9**, synthesized by Tanaka and

[9] (a) Babin, J. E.; Whiteker, G. T. Asymmetric Synthesis, World Patent, WO 9303839, 1993. (b) Whiteker, G. T.; Briggs, J. R.; Babin, J. E.; Barne, B. A. *Asymmetric Catalysis Using Bisphosphite Ligands. In Chemical Industries*; Marcel Dekker, Inc.: New York, 2003; Vol. 89, pp 359.

[10] (a) Buisman, G. J. H.; Vos, E. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Chem. Soc. Dalton Trans.***1995**, 409. (b) Buisman, G. J. H.; van der Veen, L. A.; Klootwijk, A.; de Lange, W. G. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Organometallics.* **1997**, *16*, 2929.

Nozaki.[11] Hydroformylation using binaphos **3.9** gave excellent enantioselectivity for both styrene derivatives and vinylacetate (Scheme 3.5); however, regioselectivities were typically lower compared to the chiraphite promoted reactions. The NMR studies showed that rhodium complex existed as a defined single species (**3.10**) where phosphine occupies an equatorial position and the phosphite an apical position that is *trans* to the hydride. The formation of this single reactive rhodium species **3.10** was the key to induce highly enantioselective hydroformylation.

Scheme 3.5. Asymmetric Hydroformylation of Alkenes with Binaphos

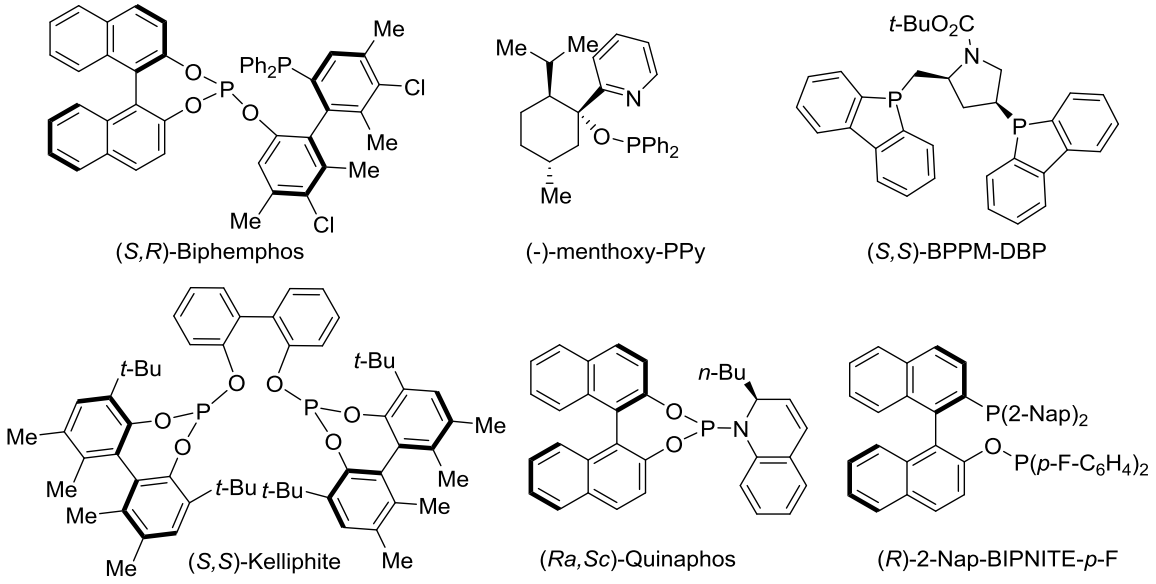


Since the discovery of chiraphite **3.5** and binaphos **3.9**, a number of effective chiral ligands have been developed for asymmetric hydrofromylation of styrene derivatives and vinylacetates (Figure 3.2). They have been thoroughly discussed in

[11] (a) Nozaki, K.; Sakai, N.; Nanno, T.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413. (b) Diéguez, M.; Pàmies, O.; Claver, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2113.

several reviews and book chapters.[12] However, asymmetric hydroformylation of monoalkyl-substituted alkenes still remains a challenging task, not only because of the difficulties in controlling regioselectivity in the absence of stabilized intermediate complex **d** (Figure 3.1) but also in controlling enantioselectivity due to the similar sizes of vinyl substitutions (Scheme 3.6, alkyl to H *vs.* Ph to H). Binaphos **3.9** might be the very first ligand used for asymmetric hydroformylation of monoalkyl-substituted alkenes (1-hexene, Scheme 3.5), and gave the corresponding branched aldehyde, 2-methylhexanal, with good enantiomeric excess as the minor regioisomer (only 1:3 branch:linear). Thus, it is of great importance to find a more effective ligand for this valuable transformation.

Figure 3.2. Selected Chiral Ligands for Asymmetric Hydroformylation of Styrenes

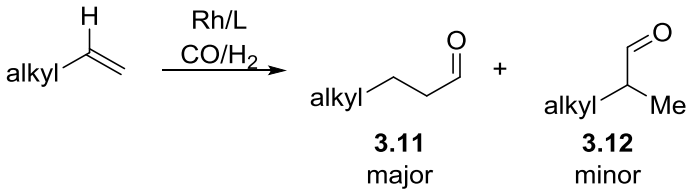


[12] For book chapters, see: (a) Nozaki, K.; Ojima, I. *In Catalytic Asymmetric Synthesis;* 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000, p 429. (b) Eilbracht, P. In *Houben-Weyl*; 4th ed., Vol. E21c. Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds; Thieme: Stuttgart, 1995; p 2488. For journal reviews, see: (c) Agbossou, F.; Carpentier, J. F.; Mortreux, A. *Chem. Rev.* **1995**, *95*, 2485. (d) Gladiali, S.; Bayon, J. C.; Claver, C. *Tetrahedron: Asymmetry* **1995**, *6*, 1453. (e) Breit, B.; Seiche, W. *Synthesis*, **2001**, 1. and reference therein.

3.2.3. Asymmetric Hydroformylation of Alkyl-substituted 1-Alkenes

In the planning stage of total synthesis of (+)-discodermolide (Chapter 2), it was realized that a readily accessible asymmetric hydroformylation of allylic ethers and related compounds would effectively streamline the synthesis of key building blocks. While a number of advances of asymmetric hydroformylation have been disclosed, the substrates have been only limited to highly activated and electronically biased substrates, such as styrene, vinylacetate and vinylamide as described above. For alkyl-substituted 1-alkenes, standard rhodium catalyzed hydroformylation is slightly linear selective due to steric interactions and lack of preference for intermediate **d** (Scheme 3.6). Though the regioselectivity can be controlled to some extent by reaction conditions, it is mainly controlled by the nature of chelating ligand.[13] Thus, it is of great importance to find an easily accessible and effective ligand for the valuable asymmetric hydroformylation of allyl ethers and related compounds. Only recently have novel chiral ligands been designed to target this set of alkene substrates in asymmetric hydroformylation.

Scheme 3.6. Hydroformylation of Monoalkyl-substituted Alkenes

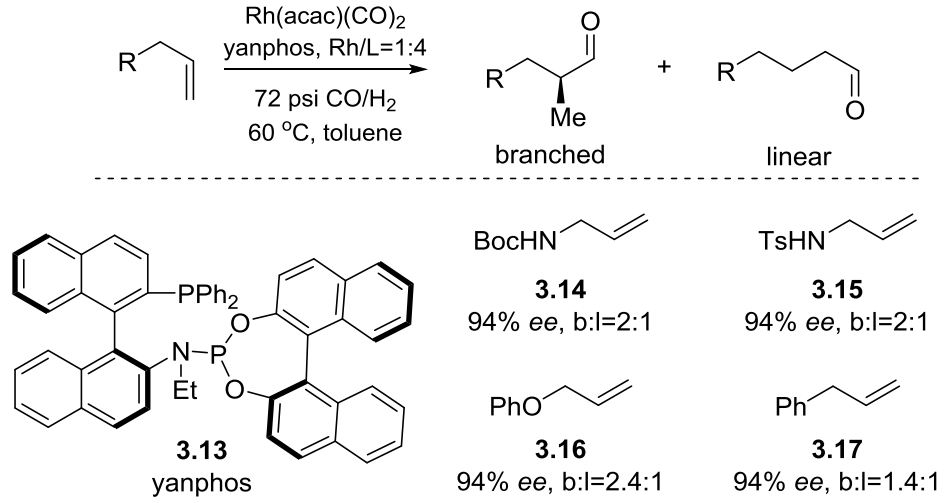


In 2010, Zhang and co-workers reported a rhodium-yanphos complex catalyzed asymmetric hydroformylation of *N*-allylamides and *N*-allylsulfonamides (Scheme 3.7).[14] Yanphos **3.13** is structurally similar to binaphos **3.11**, where an oxygen atom was replaced by a NEt fragment. Enantiomerically pure β^2-amino aldehydes were obtained

[13] Klosin, J.; Landis, C. R. *Acc. Chem. Res*, **2007**, *40*, 1251.
[14] Zhang, X. W., Cao, B. N., Yu, S. C.; Zhang, X. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 4047.

from allylamines (**3.14** and **3.15**) with moderate regioselectivity. This reaction system also worked for allyl ether **3.16** as well as allylbenzene **3.17** furnishing the corresponding branched aldehydes with good regioselection and enantiomerically excess. Unfortunately, yanphos **3.13** is only available through a seven-step synthesis from expensive (+)-NOBIN.[15]

Scheme 3.7. Asymmetric Hydroformylation of Alkenes with Yanphos

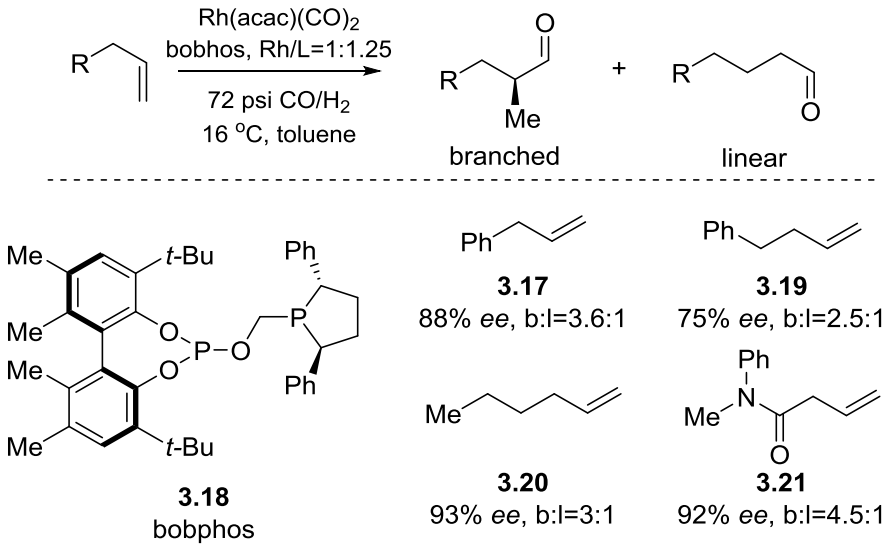


Later, a novel unsymmetrical chiral ligand, bobphos **3.18**, was designed by Clark and Cobley for asymmetric hydroformylation of various alkyl substituted 1-alkenes (Scheme 3.8).[16] Allylbenzene **3.17** and homoallylbenzene **3.19** participated in this reaction providing branched aldehydes with good regioselectivity but only moderate enantioselectivity. Importantly, non-electronically biased 1-hexene **3.20** also served as good substrate producing (+)-1-methyl hexanal with good branch to linear ratio and enantiomeric excess. The basic amide function group in **3.21** was also well-tolerated in the catalytic hydroformylation. Bobphos **3.18** is one of the first ligands generating

[15] Yan, Y.; Zhang, X. *J. Am. Chem. Soc*. **2006**, *128*, 7198.
[16] Noonan, G. M., Fuentes, J. A., Cobley, C. J.; Clarke, M. L. *Angew. Chem. Int. Ed*. **2012**, *51*, 2477.

branched aldehyde with good selectivity in hydroformylation of alkyl substituted 1-alkenes. The low reaction temperature (16°C) is necessary for good regio- and enantioselectivity, but caused incomplete conversion as well as prolonged reaction time (21-66 h). The low turnover numbers and slow reaction rate is not suitable for an industrial processes. Moreover, bobphos **3.18** is not readily accessible, and requires multistep synthesis.

Scheme 3.8. Asymmetric Hydroformylation of Alkenes with Bobphos



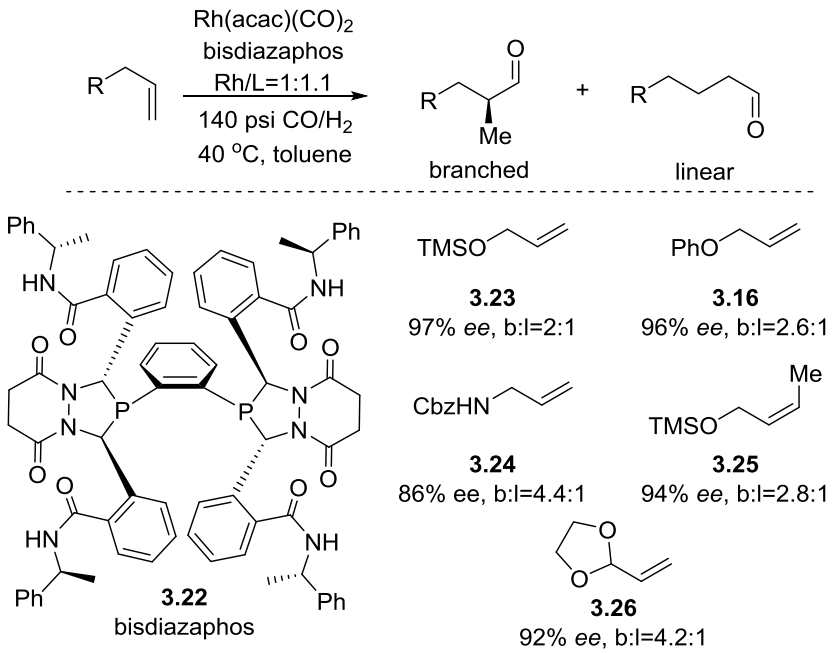
Another highly reactive and selective asymmetric hydroformylation example is the reaction using bisdiazaphos **3.22** that was developed by Landis and co-workers. Bisdiazaphos (**3.22**) mediated asymmetric hydroformylation gave excellent enantio- and regioselectivity for styrene derivatives;[17] most importantly, the reaction system was also effective for less activated terminal olefins.[18] Allyl ethers (**3.16** and **3.23**) with various protecting groups participated in this hydroformylation reaction providing β-

[17] Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5040.
[18] McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027.

hydroxylaldehydes with moderate branch selectivity and good enantiomeric excess (Scheme 3.9). Similar to Zhang's example (Scheme 3.7), optically active β^2-amino aldehydes were produced *via* asymmetric hydroformylation of allylamine **3.24**. Interestingly, TMS-protected *cis*-crotylalcohol **3.25** underwent asymmetric hydroformylation smoothly to produce corresponding chiral aldehyde with moderate regioselectivity and good enantioselectivity. Synthetically useful malondialdehyde equivalent was generated by asymmetric hydroformylation of acetal protected acrolein **3.26** with higher regioselectivity and good enantiomeric excess. Each reaction reached full conversion of starting material rapidly with turnover numbers calculated as high as 2000 h^{-1}. It is proposed that the observed high reactivity results from electron-deficient nature of bisdiazaphos, as indicated by the IR carbonyl stretching frequency of its Rh-complex. [19] Though bisdiazaphos **3.22** served as a great ligand for asymmetric hydroformylation of various terminal olefins, similar to the aforementioned ligands, it is not readily available[20] and requires multistep synthesis.

[19] Landis, C. R.; Nelson, R. C.; Jin, W.; Bowman, A. C. *Organometallics.* **2006**, *25*, 1377.
[20] Once upon a time, bisdiazaphos **3.22** and its diastereomer were commercial from Sigma-Aldrich (product number 685232 and 685259) but they were discontinued later.

Scheme 3.9. Asymmetric Hydroformylation of Alkenes with Bisdiazaphos

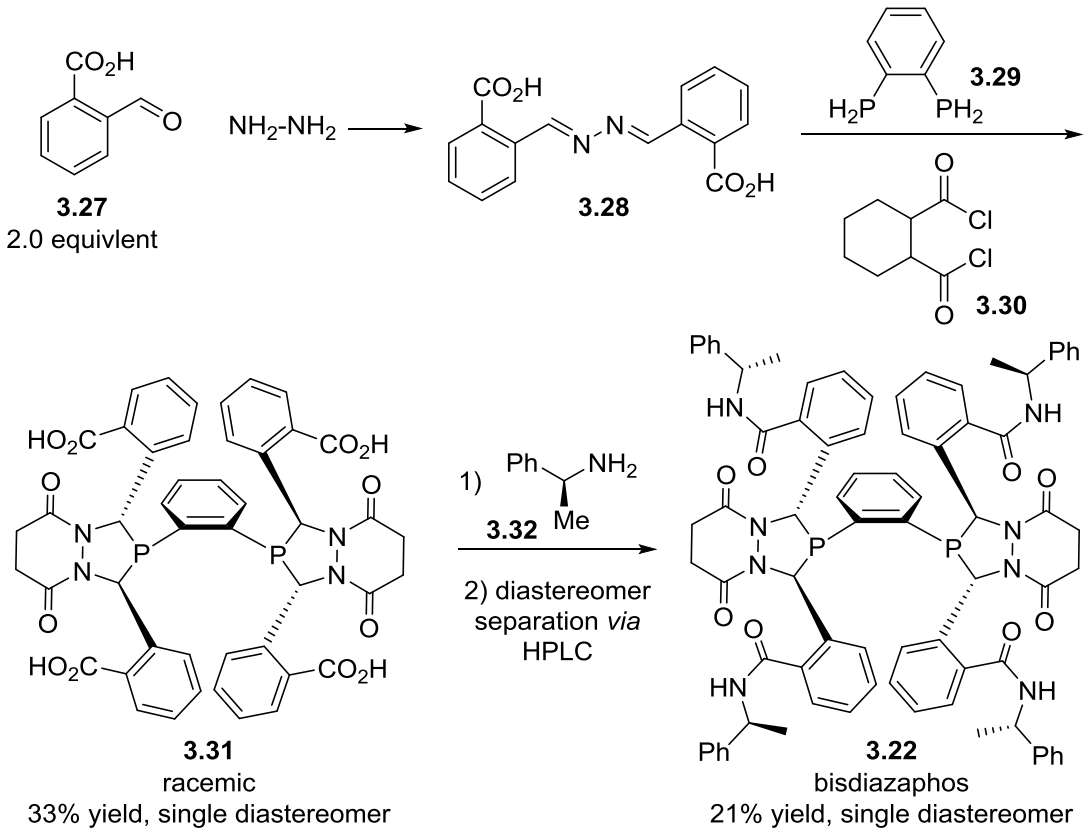


Asymmetric hydroformylation is a rapid and efficient method to construct synthetically useful building blocks from inexpensive olefins; however, it is rarely used in complex molecule synthesis.[21] It is suspected that the limited availability of efficient chiral ligands limits the broad application of asymmetric hydroformylation. The aforementioned beautifully designed chiral ligands require multistep syntheses, though they are effective ligands for asymmetric hydroformylation of 1-alkenes. For example, optically active bisdiazaphos **3.22** can be prepared in a three-step sequence starting from condensation of phthalaldehydic acid **3.27** furnishing azine **3.28** (Scheme 3.10). Subsequent cyclization of azine **3.28** with diphosphinobenzene **3.29** and di-acidchloride **3.30** provides racemic tetra-acid **3.31** as single diastereomer with only 33% yield. Derivatization of tetra-acid **3.31** with enantiomerically enriched amine **3.32** furnishes a pair of diastereomers; however, only one diastereomer is active representing

[21] (a) Ho, S.; Bucher, C.; Leighton, J. L. *Angew. Chem. Int. Ed*. **2013**, *52*, 6757. (b) Risi, R. M.; Burke, S. D. *Org. Lett*. **2012**, *14*, 2572.

match/mismatch case. Thus it is necessary to separate the two diastereomers, which requires the use of LC with a Zorbax Rx-Sil column providing more active diastereomer **3.22** with only 21% yield. Though the ligand synthesis sequence is short and straight forward from commercially available materials, the use of pyrophoric diphosphinobenzene **3.29** as well as LC separation in low yield might prevent its wide applications.

Scheme 3.10. Synthesis of Bisdiazaphos

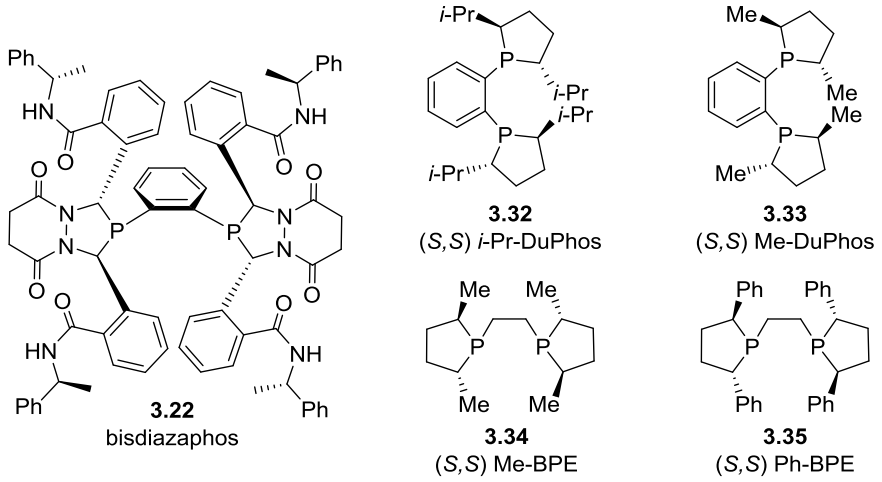


Thus, it is of great importance to find a readily accessible ligand for asymmetric hydroformylation to enable rapid construction of synthetically useful building blocks from inexpensive olefins. Moreover, such asymmetric hydroformylation would be greatly beneficial for the total synthesis of (+)-discodermolide (Chapter 2).

3.3 Development of Asymmetric Hydroformylation of Terminal Olefins with Readily Available Ligand

Considering the success of bisdiazaphos **3.22** in asymmetric hydrofromylation, we considered that a structurally and electronically similar bidentate phosphine ligand would be as effective. Thus, the bis(phospholano)benzene (DuPhos) and bis(phospholano)ethane (BPE) families of ligands appear to be logical candidates (Figure 3.3). Moreover, both enantiomers of each ligand are commercially available from various venders.[22]

Figure 3.3. Bisdiazaphos, DuPhos and BPE ligands

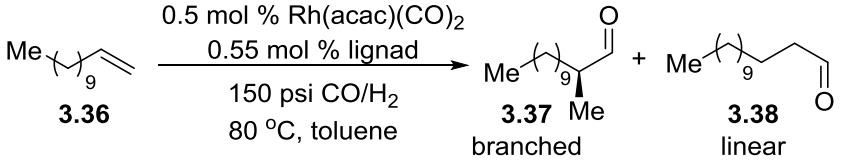


The DuPhos and BPE ligands have proved to be excellent ligands for asymmetric hydrogenation of various substrates,[23] but their use in asymmetric hydroformylation reactions has been reported only once where 1,2-bis-(2,5-diphenylphospholano)ethane (Ph-BPE) was identified as an excellent ligand for asymmetric hydroformylation of

[22] For example, 22 DuPhos and BPE ligands are available from Sigma-Aldrich, 20 from Strem Chemicals Inc., 6 from Alfa Aesar, and 5 from Acros (data as of 10/6/2014). The price may vary from different vendors.
[23] Tang, W.; Zhang, X. *Chem. Rev*. **2003**, *103*, 3029.

styrene, allylcyanide and vinyl acetate.[24] But more interesting and challenging monoalkyl-substituted alkenes, such as allyl ethers and 1-dodecene, haven't been studied. Herein, we tested several DuPhos and BPE ligands for asymmetric hydroformylation using non-electronically biased 1-dodecene as model substrate.

Table 3.1. Ligand Screening for Asymmetric Hydroformylation



entry	ligand	b:l [a]	*e.e.* % [b]
1	**3.32**	1.1:1	85
2	**3.33**	0.5:1	18
3	**3.34**	0.9:1	10
4	**3.35**	1.2:1	90

[a] branch/linear ratio were determined by ^{1}H NMR. [b] determined after conversion to its benzoate derivative.

Under conditions of 150 psi syngas ($CO:H_2$=1:1) and 80 ^oC with 0.5 mol % of $Rh(acac)(CO)_2$ and 0.55 mol % phosphine ligand, both Me-DuPhos and Me-BPE promoted hydroformylation converting 1-dodecene **3.36** to desired aldehyde **3.37** with serviceable regioselectivity, but with poor enantioselectivity (Table 3.1, entry 2 and 3). This might be attributed to the small 2,5-dimethyl substitutions on the ligand which don't provide sufficient chiral environment. As expected, changing phospholane 2,5-substituents to larger isopropyl (**3.32**) and phenyl (**3.35**) groups provided much higher enantioselectivity, 85% and 90% enantiomeric excess respectively (Table 3.1, entry 1 and 4). Ph-BPE **3.35** was identified as the most effective ligand and gave the highest

[24] Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 5834.

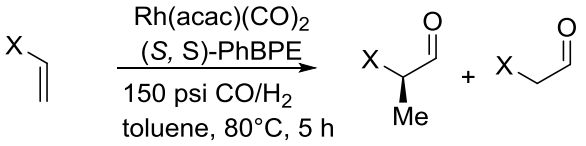
enantioselectivity and slightly better branch to linear ratio compared to other tested ligands. The high reaction temperature might cause the low but serviceable regioselectivity; however, this temperature is crucial for fast hydroformylation reaction rate. After balancing reaction regioselectivity and reaction rate, we decided to take 150 psi syngas and 80 ^{o}C in toluene as optimum reaction conditions and Ph-BPE **3.35** as the best ligand.

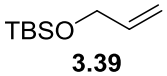
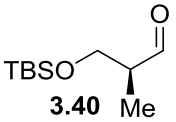
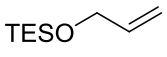
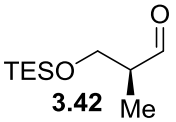
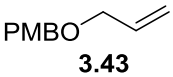
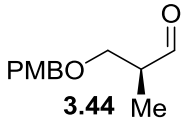
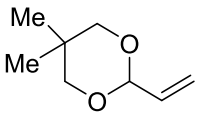
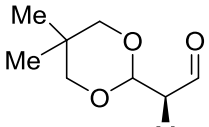
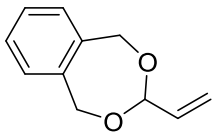
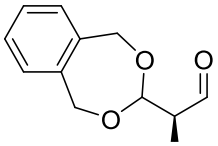
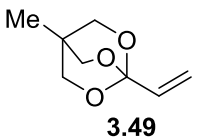
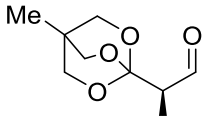
We moved forward to examine the substrate scope of this rhodium catalyzed asymmetric hydroformylation reaction. Optically pure β-siloxyl aldehydes (**3.40** and **3.42**) were obtained with higher regioselectivity by subjecting slightly electronically biased TBS- and TES-protected allyl alcohol (**3.39** and **3.41**) to standard reaction conditions (Table 3.2, entry 1 and 2). The branched to linear aldehyde ratio for TBS-ether **3.39** is almost doubled compared to the bisdiazaphos mediated asymmetric hydroformylation (Table 3.2, entry 1).[19] *Para*-methoxylbenzyl allyl ether **3.43** was found to produce aldehyde **3.44** with even higher regioselectivity while maintaining a high level of enantioselectivity (Table 3.2, entry 3). The good regioselection with allyl ether (**3.39**, **3.41** and **3.43**) is likely due to the stabilization of the partial negative charge at internal carbon by oxygen functionality,[25] enhancing the preference of intermediate **d** after hydrometalation (III) (Figure 3.1). Some protecting groups for allyl alcohols are not suitable for this asymmetric hydroformylation, such as acetate, mesylate and tosylate, which might be attributed to the formation of corresponding rhodium π-allyl intermediate in the presence of a good allylic leaving group.[26] Acrolein-derived acetals (**3.47** and **3.49**)

[25] Ojima, I. *Chem. Rev.* **1988**, *88*, 1011.
[26] (a) Tsuji, J.; Minami, I.; Shimidzu, I. *Tetrahedron Lett.* **1984**, *25*, 5157. (b) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc*. **1998**, *120*, 5581. (c) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc*. **2001**, *123*, 4609.

gave optically active aldehydes (**3.48** and **3.50**) that are equivalent to synthetically useful malondialdehydes in good branch to linear ratio (>10:1) (Table 3.2, entry 4 and 5). Vinyl orthoester **3.49**[21b] was smoothly converted to desired aldehyde **3.50** with excellent regioselectivity (Table 3.2, entry 6), which served as a key starting material for the synthesis of oxidation-resistant discodermolide analog (Chapter 2).

Table 3.2. Asymmetric Hydroformylation of Allyl Ethers, Allylacetals and Vinyl Orthoester[a]

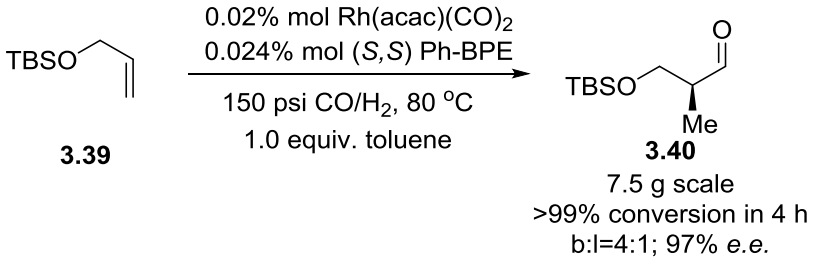


entry	substrate	product	conv. (%)	b:l[b]	*e.e.* (%)
1	 **3.39**	 **3.40**	99	3.9:1 *2.0:1*[c]	97 *96*[c]
2	 **3.41**	 **3.42**	99	3.5:1	90
3	 **3.43**	 **3.44**	99	5.5:1	93
4	 **3.45**	 **3.46**	99	12:1	93
5	 **3.47**	 **3.48**	99	10:1	93
6	 **3.49**	 **3.50**	99	15:1 *12:1*[c]	89 *93*[c]

[a] reactions preformed with 0.5 mol % Rh cat. and 0.55 mol % ligand, [substrate] =1.0 M. [b] b:l ratios are determined by ^{1}H NMR anaylsis. [c] Data reported in literature using bisdiazaphos.[18,21b]

It is important to test such asymmetric hydroformylation on large scale to facilitate organic syntheses. Pleasingly, no erosion in stereoselection was observed when 7.5 grams of allyl ether **3.39** was subject to standard hydroformylation conditions with lower catalyst loading (0.02 mol %) and little organic solvent (1.0 equivalent) (Scheme 3.11). Moreover, the reaction reached full conversion in 4 hours (indicated by syngas uptake graph) and the turnover frequency was calculated as 1250 h^{-1}. Starting from commodity allyl alcohols and commercially available chiral ligand, this method provides an attractive two-step route to large quantities of synthetically important β-hydroxyl aldehyde **3.40**, which was historically prepared in a three-step sequence from fairly expensive Roche ester (~$20/g from Sigma-Aldrich).[27] Thus, the advantage of asymmetric hydroformylation was fully demonstrated in the Roche ester-free synthesis of (+)-discodermolide (Chapter 2).

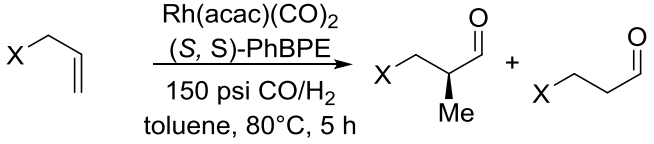
Scheme 3.11. Multigram Scale Asymmetric Hydroformylation

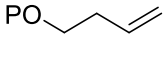
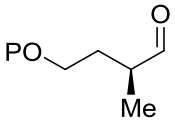
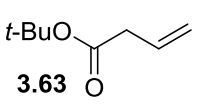
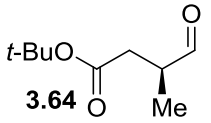
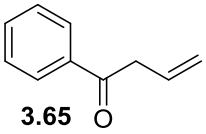
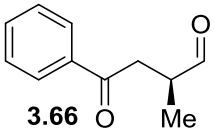
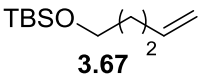
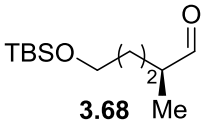


[27] For selected examples, see: (a) Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654. (b) Smith, A. B., III; Adams, C. M.; Barbosa, S. A. L.; Degnan, A. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12042. (c) Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Koch, G.; Kuesters, E.; Daeffler, R.; Osmani, A.; Seeger-Weibel, M.; Schmid, E.; Hirni, A.; Schaer, K.; Gamboni, R.; Bach, A.; Chen, S.; Chen, W.; Geng, P.; Jagoe, C. T.; Kinder, F. R., Jr.; Lee, G. T.; McKenna, J.; Ramsey, T. M.; Repic, O.; Rogers, L.; Shieh, W.-C.; Wang, R.-M.; Waykole, L. *Org. Process Res. Dev.* **2004**, *8*, 107. (d) Lawhorn, B. G.; Boga, S. B.; Wolkenberg, S. E.; Colby, D. A.; Gauss, C.-M.; Swingle, M. R.; Amable, L.; Honkanen, R. E.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 16720.

Encouraged by the reactions of allyl alcohol and acrolein derived terminal olefins, we investigated much less electronically biased and more challenging substrates (Table 3.3). Optically active γ-hydroxyl aldehydes were obtained with moderate regioselectivity and high levels of enantiomeric excess from homoallyl alcohol derivatives (Table 3.3, entry 1). Homoallylic alcohols with more electron withdrawing protecting groups were found to give higher branch to linear ratios (TFA (**3.61**)>Bz (**3.57**)>TBS (**3.51**)). Substrates **3.63** and **3.65** with ketone and ester oxidation state at homoallylic position further enhanced regioselectivity and maintained excellent enantioselectivity due to the stronger electron withdrawing nature of the substitutions (Table 3.3, entry 2 and 3). Bis-homoallylic alcohol-derived TBS-ether **3.67** provided the same regioselectivity as 1-dodecene **3.36**, which indicated that the terminal olefin is barely disturbed by hydroxyl functionality at remote bis-homoallylic position in this hydroformylation reaction (Table 3.3, entry 4).

Table 3.3. Asymmetric Hydroformylation of Less Electronically Biased 1-Alkenes[a]



entry	substrate	product	conv.(%)	b:l[b]	*e.e.* (%)
1					
	P=TBS **3.51**	**3.52**	99	2.2:1	95
	P=PMB **3.53**	**3.54**	99	2.3:1	86
	P=Ac **3.55**	**3.56**	99	2.2:1	90
	P=Bz **3.57**	**3.58**	99	2.6:1	92
	P=THP **3.59**	**3.60**	99	2:1	78
	P=TFA **3.61**	**3.62**	99	3:1	ND[c]
2			99	5.5:1	90
3			99	3.9:1	ND[c]
4			99	1.2:1	90

[a] reactions preformed with 0.5 mol % Rh cat. and 0.55 mol % ligand, [substrate]=1.0M. [b] branch to linear ratios were determined by ^{1}H NMR anaylsis. [c] ND=not determined, because of instability of related aldehyde products.

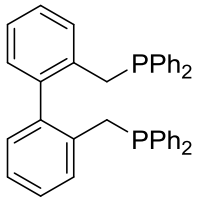
As mentioned above, the observed good reactivity and regioselectivity of hydroformylation were not only due to intrinsic substrate preference but also a result of the nature of Ph-BPE ligand **3.35**. The high reactivity of Ph-BPE ligand might be attributed to the presence of electron-withdrawing phenyl rings that reduces overall basicity of the phosphine center; it is known that electron-poor phosphine ligands lead to more active catalysts in Rh-catalyzed hydroformylation.[3] According to the *natural bite*

angle concept introduced by Casey and Whitaker,[28] bidentate phosphine ligands with larger natural bite angle (e.g. BISBI **3.69**, Xantphos **3.70**) gives a higher linear to branched ratio in hydroformylation (Table 3.4). This is because ligand with large bite angle (≥120°) will bind equatorial/equatorial at rhodium center, while ligand with small bite angle will bind equatorial/axial at rhodium center. Though the natural bite angle was calculated based on molecular mechanics methods, it is quite close to the bite angle measured from X-ray crystallography of corresponding metal complex. For example, the natural bite angle of dppe is 84.5° in rhodium complex while the measured bite angle is 85.8°. Thus, it is safe to say that the natural bite angle of Ph-BPE is close to the measured bite angle, 85.5°,[29] and this small bite angle would disfavor formation of linear product rendering higher branched to linear ratio. Combination of large 2,5-phenyl groups on phopholano ring, a less basic phosphine center and a small bite angle makes Ph-BPE an effective ligand for asymmetric hydroformylation reactions. Moreover, both enantiomers of the ligand are commercially available from various venders, which could make asymmetric hydroformylation a powerful tool in complex molecule syntheses.

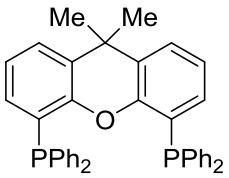
[28] (a) Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavey, J. A.; Powell, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 5535. (b) Casey, C. P.; Whiteker, G. T. *Isr. J. Chem.* **1990**, *30*, 299. (c) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519.
[29] Measured from X-ray structure reported in ref. 24.

Table 3.4. Bite Angle and Regioselectivity of Phosphine Ligands[30]

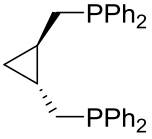
ligand	b:l	natural bite angle	measured bite angle
BISBI **3.69**	1:66.5	112.6	122.2
Xanphos **3.70**	1:53	111.7	107.1
T-BDCP **3.71**	1:12.1	106.6	-
DIOP **3.72**	1:8.5	102.2	97.6
dppe **3.73**	1:2.4	84.5	85.8
Ph-PBE **3.35**	1.2:1	-	85.5[29]



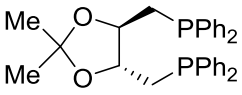
3.69
BISBI



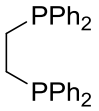
3.70
Xantphos



3.71
T-BDCP



3.72
DIOP

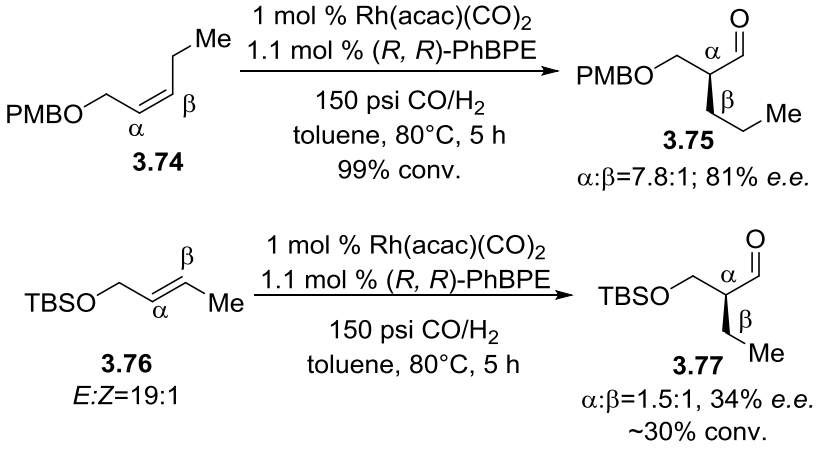


3.73
dppe

The Ph-BPE mediated asymmetric hydroformylation is not limited to terminal olefins, c*is*-allyl alcohol-derived PMB ether **3.74** also participated in this reaction to furnish optically pure aldehyde **3.75** with good regioselectivity (α:β = 7.8:1) (Scheme 3.12). This is one of the rare examples of regioselective asymmetric hydroformylation for internal olefins. Unfortunately, *trans*-crotyl alcohol-derived TBS-ether **3.76** gave roughly equal amount of two regioisomeric aldehydes with incomplete conversion and significantly diminished enantioselectivity (determined by the Mosher ester[31] prepared from aldehyde **3.63**).

[30] van Leeuwen, P.W.N.M. *Homogeneous Catalysis: Understanding the Art*, Springer; 2004.
[31] (a) Dull, D. L.; Mosher, H. S. *J. Am. Chem. Soc.* **1967**, *89*, 4230. (b) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem*. **1969**, *34*, 2543. (c) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

Scheme 3.12. Asymmetric Hydroformylation of Internal Olefins

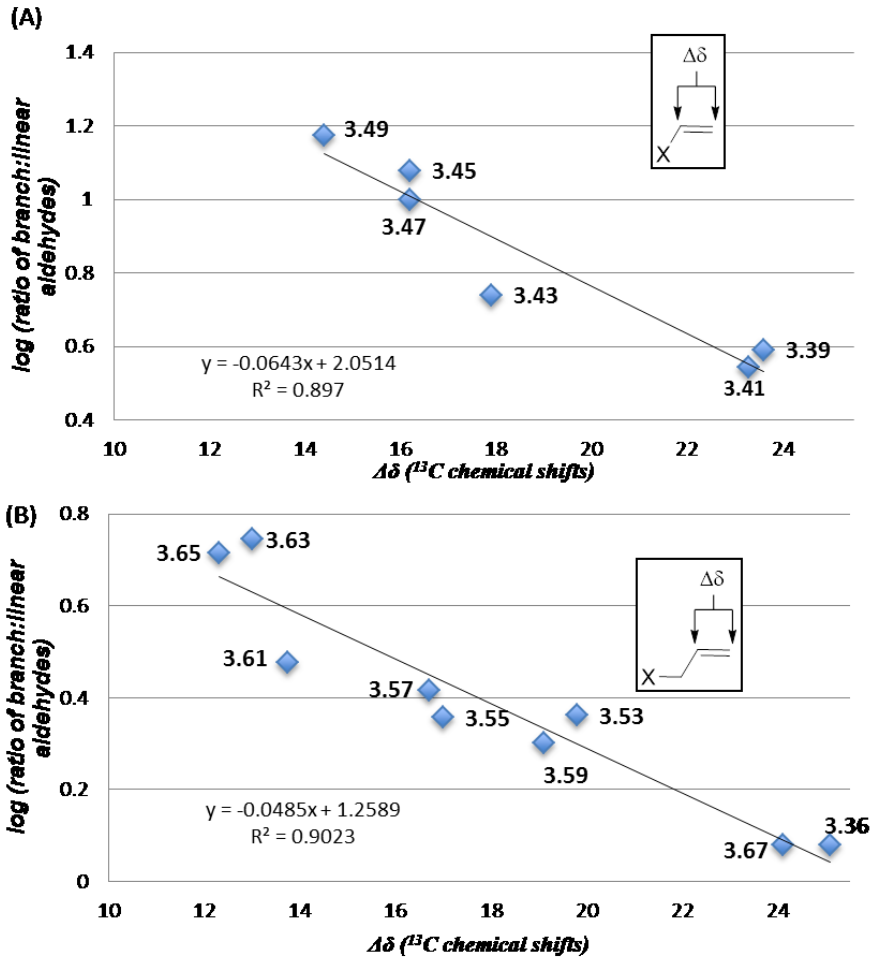


Good enantioselectivity of Rh/Ph-BPE catalyzed asymmetric hydroformylation has been observed for a broad range of substrates. In contrast, regioselectivity is highly substrate dependent and ranged from 15:1 to 1:1. As mentioned previously, the presence of an electron-withdrawing group would polarize the olefin and stabilize negative charge at internal carbon enhancing the preference for the intermediate **d** after hydrometalation (III) (Figure 3.1); this increases the hydroformylation branch selectivity. Thus, it is anticipated that the regioselectivity correlates to substituent's electronic property. ^{13}C NMR spectroscopy is a useful tool to study substitution effect on the electronic environment of a carbon,[32] and it appears reasonable to study the relationship between regioselectivity and relative ^{13}C ($\Delta\delta$ ^{13}C) chemical shifts of each terminal alkene (Table 3.2 and Table 3.3). It was found that $\Delta\delta$ ^{13}C is affected by substituents' electronic properties: the more electron withdrawing substituents that are closer to the olefin result smaller $\Delta\delta$ ^{13}C. Then, the plots of regioselectivity and $\Delta\delta$ ^{13}C for different substrates (Table 3.2 and Table 3.3) are shown in Figure 3.4. Good correlations have been found in

[32] (a) Kalinowski, H. O.; Berger, S.; Braun, S. *Carbon-13 NMR spectroscopy*; Wiley: Chichester, 1988; Chapter 3, p 92. (b) Sohar, P. *Nuclear Magnetic Resonance Spectroscopy*; CRC Press: Boca Raton, 1983; Vol. 2, Chapter 4, p 145. (c) Mei, T. S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 6830.

both cases revealing that a substrate's electronic property governs the regioselectivity, though other scenarios can't be ruled out. A steeper slope of allyl alcohol derivatives (Figure 3.4A) indicates that substitution at the allylic position has a larger effect on polarizing olefin compared to the substitution at the homoallylic position (Figure 3.4B) due to closer proximity to the double bond.

Figure 3.4. Plots of Δδ ^{13}C Chemical Shifts v.s. Regioselectivity (A: Table 3.2, B: Table 3.3)



3.4 Conclusion

A rhodium complex with a commercially available Ph-BPE ligand has proved to be an efficient catalyst for asymmetric hydroformylation of lowly activated and non-electronically biased terminal olefins. A number of terminal alkenes, even including an internal olefin, participate in this reaction to furnish synthetically useful and optically active aldehydes with moderate to high regioselectivities. This reaction works equally well on multigram scale with low catalyst loading while maintaining fast reaction rate and regioselection. Furthermore, good correlations are found between substitutions' electronic properties and branched to linear selectivities. This asymmetric hydroformylation reaction could greatly benefit organic syntheses by rapidly constructing synthetically important chiral aldehyde building blocks from inexpensive alkenes. It is also anticipated that the development of this asymmetric hydroformylation with readily accessible catalyst would encourage its use in fine chemical and complex molecule syntheses as well as the preparation of biologically active compounds.

3.5. Experimental Procedure

General Information

^{1}H NMR spectra were recorded on a Varian Gemini-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as the following: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent), and coupling constants (Hz). Coupling constants are reported to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded on a Varian Gemini-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.23 ppm). Infrared (IR) spectra were recorded on a Burker alpha spectrophotometer, ν_{max} cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectrometry (ESI) was performed at the Mass Spectrometry Facility, Boston College.

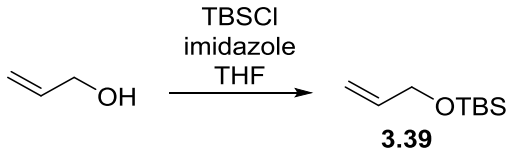
Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230×450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$) in water, 2,4-dinitrophenylhydrazine (2,4-DNP) in water/ethanol or phosphomolybdic acid (PMA) in ethanol. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. Analytical chiral supercritical

fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF), toluene, diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. by passing through two activated alumina columns after being purged with argon. Hydroformylation reactions were performed in an Argonaut Technologies Endeavor® Catalyst Screening System or 100-600 mL pressure vessel by Parr Instrument Company with a gage block using 1:1 H_2/CO supplied by Airgas, Inc. (Acetylacetonato)dicarbonylrhodium (I) [$Rh(acac)(CO)_2$] and (−)-1,2-Bis((2*R*,5*R*)-2,5-diphenylphospholano)ethane [(*S,S*)-Ph-BPE] were purchased from Strem Chemicals, Inc. and used without further purification. All other reagents were purchased from Aldrich, Alfa Aesar, or Fisher and used without further purification.

I. Preparation of Terminal Olefins

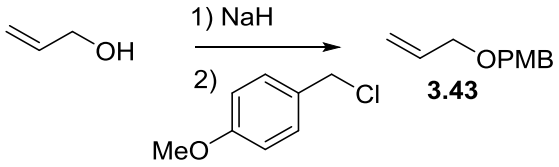
Preparation of (Allyloxy)(tert-butyl)dimethylsilane



3.39

(Allyloxy)(*tert*-butyl)dimethylsilane **3.39** (Table 3.2, entry 1) was prepared using known procedure and all spectrum data are in accordance with literature report.[33] Similar procedure was used to prepare (allyloxy)triethylsilane **3.41** (Table 3.2, entry 2).

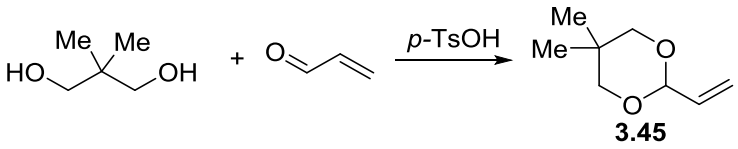
Preparation of 1-((allyloxy)methyl)-4-methoxybenzene



3.43

1-((Allyloxy)methyl)-4-methoxybenzene **3.43** (Table 3.2, entry 3) was prepared using known procedure and all spectrum data are in accordance with literature report.[34]

Preparation of 5,5-dimethyl-2-vinyl-1,3-dioxane



3.45

Acetal **3.45** (Table 3.2, entry 4) was prepared using known procedure and all spectrum data are in accordance with literature report.[35]

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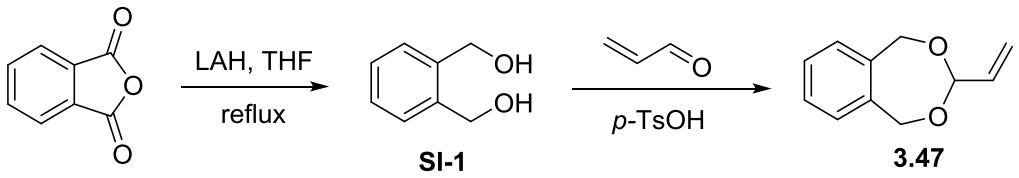
[33] Su, C. C.; Williard, P. G. *Org. Lett.* **2010**, *12*, 5378.
[34] Chênevert, R.; Dasser, M. *J. Org. Chem.* **2000**, *65*, 4529.
[35] Doumèche, B.; Archelas, A.; Furstoss, R. *Adv. Synth. Catal*. **2006**, *348*, 1948.

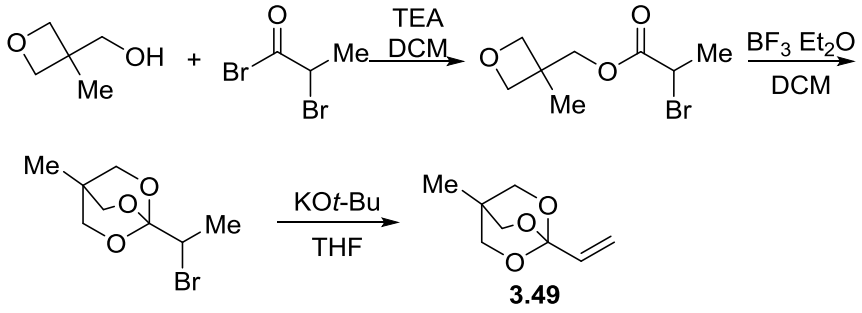
Preparation of 3-vinyl-1,5-dihydrobenzo[e][1,3]dioxepine



1,2-Benzenedimethanol **SI-1** was prepared according to literature procedure.[36]

Diol (3.3 g, 23.9 mmol) and catalytic *p*-TsOH were dissolved in dry CH_2Cl_2 (12 mL) in a 50 mL round bottom flask suspended with $MgSO_4$ under nitrogen. Acrolein (1.59 mL, 23.9 mmol) was added dropwise to the mixture at room temperature and stirred overnight. The resulting mixture was filtered and concentrated. The residue was purified by silica gel chromatography to afford the titled compound **3.47** (Table 3.2, entry 5) as colorless oil (3.3 g, 79%). All spectrum data are in accordance with literature report.[37]

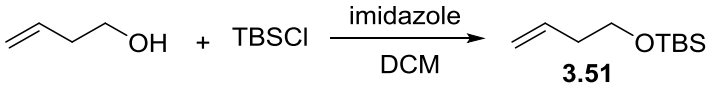
Preparation of 4-methyl-1-vinyl-2,6,7-trioxabicyclo[2.2.2]octane



Vinyl-OBO **3.49** (Table 3.2, entry 6) was prepared using known sequence from commercial oxetane and all spectrum data are in accordance with literature report.[21b]

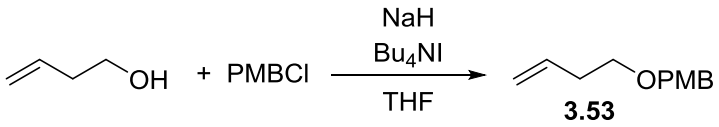
[36] Steffen, J.; Lei, X. G.; Li, W.; Liu, Z. -Q.; Turro, N. J.; Ottaviani, M. F.; Abrams, L. *J. Org. Chem.* **2002** , *67*, 2606.
[37] Arab, K. E.; Hanan, A. Q,; Patrick, M. H. *J. Organomet. Chem.* **2002**, *656*, 168.

Preparation of (but-3-en-1-yloxy)(tert-butyl)dimethylsilane



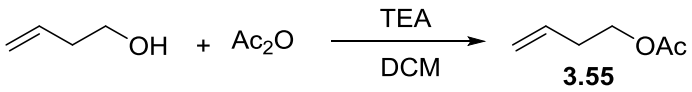
Homoallyl ether **3.51** (Table 3.3, entry 1) was prepared using known procedure and all spectrum data are in accordance with literature report.[38]

Preparation of 1-((but-3-en-1-yloxy)methyl)-4-methoxybenzene



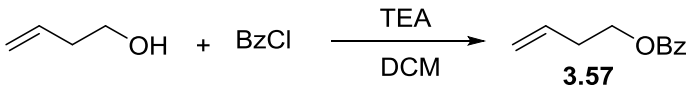
Homoallyl ether **3.53** (Table 3.3, entry 1) was prepared using known procedure and all spectrum data are in accordance with literature report.[39]

Preparation of 3-buten-1-yl acetate



Homoallyl acetate **3.55** (Table 3.3, entry 1) was prepared by known procedure and all spectrum data are in accordance with literature report.[40]

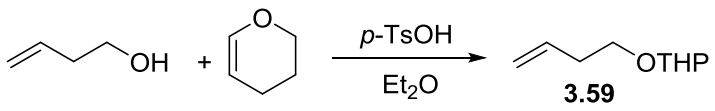
Preparation of but-3-en-1-yl benzoate



[38] Ghosh, A. K.; Li, J. -F. *Org. Lett.* **2009**, *11*, 4164.
[39] Raghavan, S.; Krishnaiah, V. *J. Org. Chem.* **2010**, *75*, 748.
[40] Fürstner, A.; Müller, T. *Synlett.* **1997**, 1010.

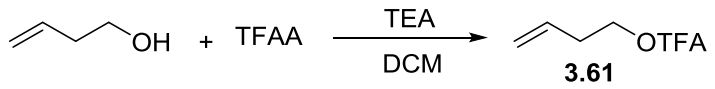
Homoallyl benzoate **3.57** (Table 3.3, entry 1) was prepared by known procedure and all spectrum data are in accordance with literature report.[41]

Preparation of 2-(but-3-en-1-yloxy)tetrahydro-2H-pyran



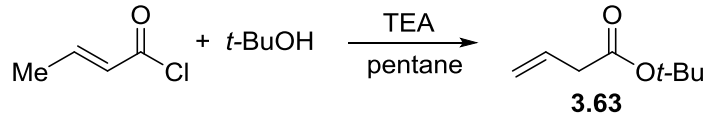
Tetrahydropyran **3.59** (Table 3.3, entry 1) was prepared using known procedure and all spectrum data are in accordance with literature report.[42]

Preparation of but-3-en-1-yl 2,2,2-trifluoroacetate



Trifluoroacetate **3.61** (Table 3.3, entry 1) was prepared using known procedure and all spectrum data are in accordance with literature report.[43]

Preparation of but-3-enoic acid tert-butyl ester



t-Butyl ester **3.63** (Table 3.3, entry 2) was prepared using known procedure and all spectrum data are in accordance with literature report.[44]

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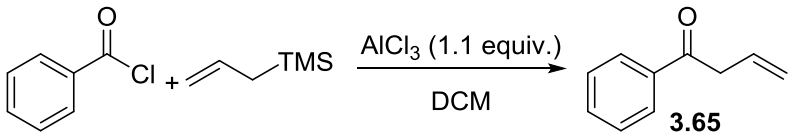
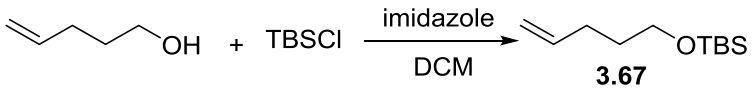
[41] Zhang, M.; Vedanthanm, P.; Flynn, D. L.; Hanson, P. R. *J. Org. Chem.* **2004**, *69*, 8340.
[42] Hernandez, D.; Nielsen, L.; Lindsay, K. B.; Lopez-Garcia, A.; Bjerglund, K.; Skrydstrup, T.; *Org. Lett.* **2010**, *12*, 3528.
[43] Abd El Samii, Z. K. M.; Al Ashmawy, M. I.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 1*, **1988**, 2509.
[44] Ramachandran, P.V.; Nicponski, D.; Kim, B. *Org. Lett.* **2013**, 15, 1398.

Preparation of 1-phenyl-but-3-en-1-on



To an oven dried 50 mL round bottom flask with stir bar was added aluminum chloride (730.0 mg, 5.5 mmol), capped with septa and purged with N_2. To this was added CH_2Cl_2 (20 mL) followed by dropwise addition of benzoyl chloride (0.58 mL, 5.0 mmol). The reaction was allowed to stir for 20 minutes followed by dropwise addition of allyltrimethylsilane (0.96 mL in 2.0 mL CH_2Cl_2, 6.0 mmol). The reaction was allowed to stir for 4 hours at room temperature. Upon completion, the reaction mixture was quenched with ice-cold deionized water and extracted three times with CH_2Cl_2. Organic layers were combined, dried over magnesium sulfate, concentrated *in vacuo* and purified on silica gel (30:1 pentane: diethyl ether) to afford a clear, colorless oil (866.4 mg, quantitative yield) (Table 3.3, entry 3). R_f = 0.31 (30:1 pentane: diethyl ether, stain in $KMnO_4$). All spectral data are in accordance with the literature.[45]

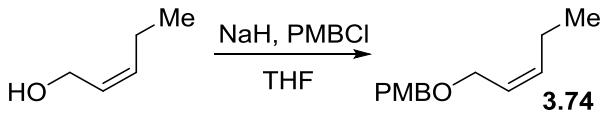
Preparation of (1,1-dimethylethyl)(dimethyl)(4-pentenyloxy)silane



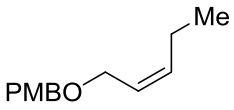
Bis-homoallyl ether **3.67** (Table 3.3, entry 4) was prepared using literature procedure and all spectrum data are in accordance with literature report.[46]

[45] Moriyama, K.; Takemura, M.; Togo, H. *J. Org. Chem.* **2014**, *79*, 6094.
[46] (a) Kovtonyuk, V.N.; Kobrina, L.S.; Gatilov, Y.V.; Bagryanskaya, I.Y.; Fröhlich, R.; Haufe, G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1929. (b) Kwan, E. E.; Scheerer, J. R.; Evans, D. A. *J. Org. Chem.* **2013**, 78, 175.

Preparation of Internal Cis-Allyl Ether



A flamed dried 100 mL round bottom flask with stir bar was charged with NaH (360 mg, 15 mmol) and 20 mL THF under N_2. After cooling to 0°C, *cis*-2-penten-1-ol (1.1 mL, 11 mmol) was added dropwise *via* syringe, which was allowed to stir at 0°C for 45 min. Then Bu_4NI (50 mg, catalytic amount) and PMBCl (1.4 mL, 10 mmol) were added sequentially at 0 °C, and the solution was allowed to warm to room temperature and stir overnight. The reaction was quenched with NH_4Cl aqueous solution and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by silica gel chromatography (diethyl ether:hexanes = 1:10) to afford **3.74** as a clear, colorless oil. R_f = 0.53 (6:1 hexanes: diethyl ether, stain in $KMnO_4$).

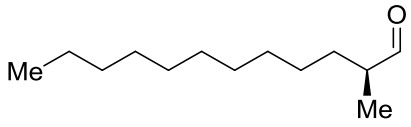


(*Z*)-1-Methoxy-4-((pent-2-en-1-yloxy)methyl)benzene (Scheme 3.11, 3.74). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (2H, d, *J* = 9.5 Hz), 6.88 (2H, d, *J* = 9.0 Hz), 5.60-5.54 (2H, m), 4.44 (2H, s), 4.04 (2H, d, *J* = 6.0 Hz), 3.81 (3H, s), 2.06 (2H, qd, *J* = 7.5, 7.5 Hz), 0.97 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.4, 135.6, 130.8, 129.6, 125.7, 114.0, 71.9, 65.5, 55.5, 21.1, 14.4; IR (neat): 3011 (w), 2836 (w), 1613 (m), 1513 (s), 1463 (w), 1302 (m), 1247 (s), 1172 (m), 1082 (s), 1036 (s), 820 (s) cm^{-1}.

II. Asymmetric Hydroformylation Reactions

Representative Procedure A: (Endeavor, 0.5% catalyst loading): Reactions were conducted in an Argonaut Endeavor® reactor system which has eight reactor wells. Each well to be used was charged with approximately 0.5 mL of toluene and an oven dried glass vial placed in each well. The Endeavor was sealed and purged with nitrogen (4 x 100 psi). Meanwhile an oven-dried two dram vial in dry box under an argon atmosphere was charged with alkene (1.0 mmol) and 0.5 mL of toluene followed by 0.5 mL of a rhodium/ligand stock solution (0.010 M $Rh(acac)(CO)_2$/0.011 M (*S,S*)-Ph-BPE in toluene). The reaction mixture was then taken up in a syringe, removed from dry box and injected into the Endeavor. After injection the Endeavor was purged with nitrogen (1 x 100 psi), stirring at 250 rpm, and heated and held at 80 °C for 10 min. Stirring was stopped and the Endeavor charged with 150 psi of syn-gas (1:1 CO/H_2), stirring was brought to 700 rpm and heated to 80 °C. When the reaction was complete the Endeavor was vented, cooled and the vials were removed.

Representative Procedure B: (Endeavor, lower catalyst loading and less solvent): similar to representative procedure A but with different amount of olefin and solvent with lower catalyst loading.

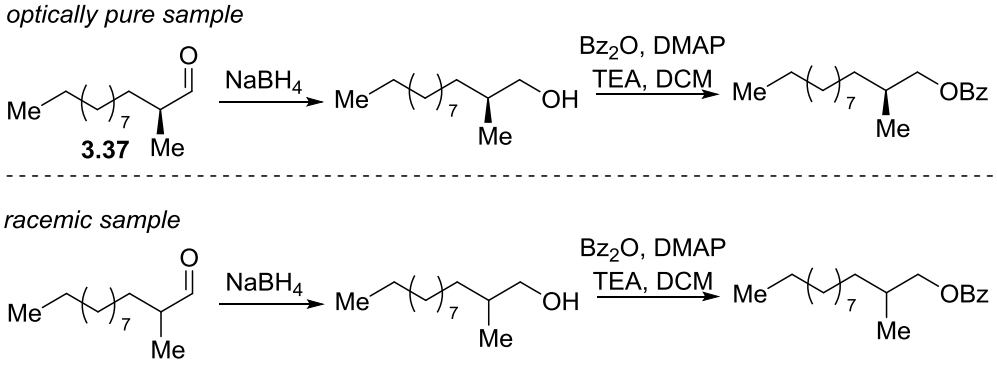


(*S*)-2-Methyldodecanal (Table 3.1, entry 4): The titled compound **3.37** was prepared with *Representative Procedure A*, on a 1.0 mmol scale with 1-dodecene **3.36**. The crude reaction mixture was purified on silica gel (100% pentane to 40:1 pentane: diethyl ether) to afford a clear

colorless oil (mixture of branched and linear isomers). R_f = 0.07 (40:1 pentane: diethyl ethere, stain in 2,4-DNP). $[\alpha]^{22}_D$ = +38.667 (*c* = 0.421, $CHCl_3$, *l* = 50 mm). Spectral data are in accordance with literature.[47]

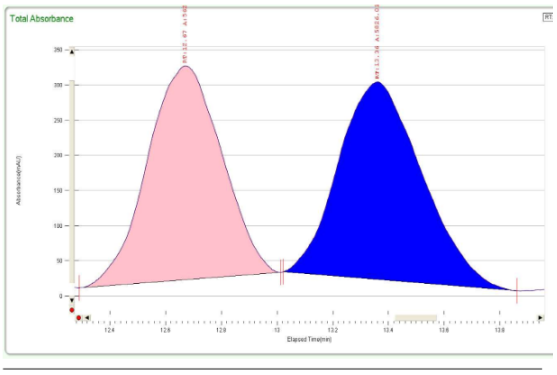
Analysis of Stereochemistry:

The titled compound **3.37** was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived benzoate. Absolute stereochemistry was determined by analogy to the optical rotation of (*S*)-2-methyldecanal reported in the literature.[48]



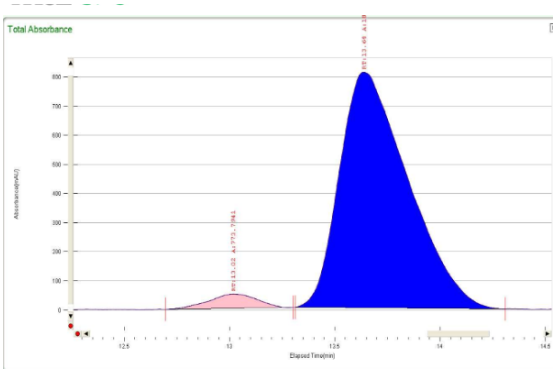
[47] Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372.
[48] Oppolzer, W.; Darcel, C.; Rochet, P.; Rosset, S.; Brabander, J. D. *Helv. Chim Acta* **1997**, *80*, 1319.

Chiral SFC (Chiralpak, AD-H, 35 °C, 3 mL/min, 2% mixed solvent (Isopropanol:hexane = 1:1) 100 bar, 210-270 nm) – analysis of benzoate.



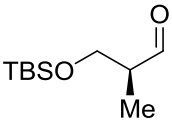
Enatnioenriched Sample

Peak Info			
Peak No	% Area	Area	RT (min)
1	49.1023	5620.4964	12.67
2	50.8977	5826.0112	13.36
Total:	100	11446.5076	



Racemic Sample

Peak Info			
Peak No	% Area	Area	RT (min)
1	4.057	773.7941	13.02
2	95.943	18299.1306	13.64
Total:	100	19072.9247	

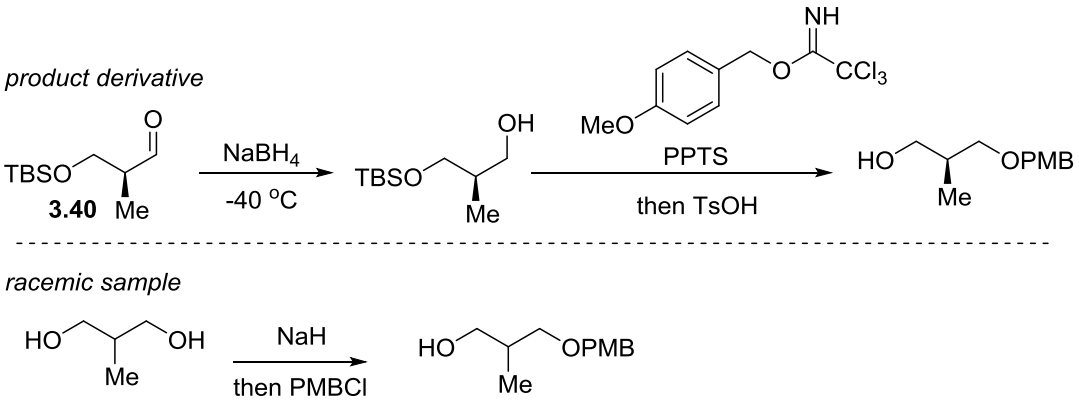


(*S*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-methylpropanal. (Table 3.2, 3.40). *Representative Procedure B* was applied with olefin **3.39** (7.7 g, 45 mmol), $Rh(acac)(CO)_2$ (4.6 mg, 0.018 mmol), (*S,S*)-Ph-BPE (17.4 mg, 0.022 mmol) and toluene (5.1 mL). Reaction reached full conversion after 8 h. (b:l = 3.8:1, 97% *e.e.*). The crude reaction mixture was purified on silica gel (hexane:diethyl ether = 20:1) to afford a clear colorless oil. $[\alpha]_D^{21}$ = +31.942 (*c* = 0.72, $CHCl_3$, *l* = 50 mm). All spectrum data are in accordance with literature.[49]

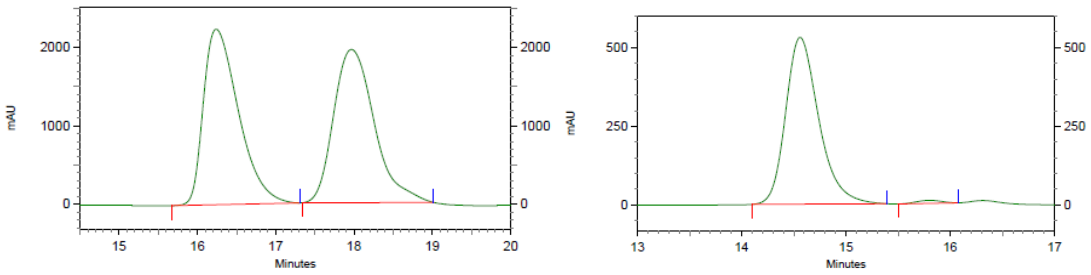
[49] Altendorfer, M.; Raja, A.; Sasse, F.; Irschikc, H.; Menche, D. *Org. Biomol. Chem.* **2013**, *11*, 2116.

Analysis of Stereochemistry

The titled compound **3.40** was converted to the corresponding *p*-methoxybenzyl ether as shown below. The resulting benzyl ether was compared to racemic material prepared from 2-methyl-propan-1,3-diol. Absolute stereochemistry was assigned by comparing optical rotation to literature $[\alpha]_D^{22} = +19.5$ (c = 1.00, $CHCl_3$, l = 50 mm).[49] Literature (the other enantiomer) $[\alpha]_D^{23} = -34.6$ (c = 1.0, $CHCl_3$)).[18]

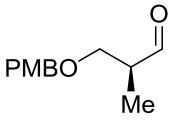


Chiral HPLC (Chiralpak, AD-H, 25 °C, 3 mL/min, 5% Isopropanol in hexane, 220 nm) – analysis of benzyl ether.



VWD: Signal A, 220 nm Results

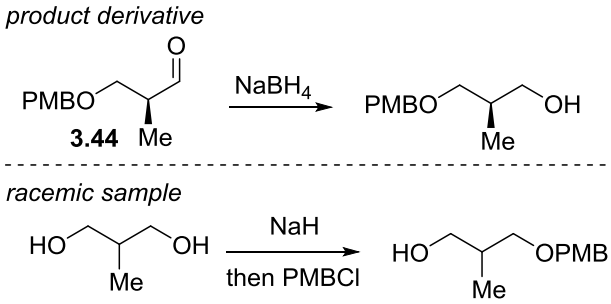
Retention Time	Area	Area %	Height	Height %
14.560	196559679	98.65	8892358	98.20
15.803	2689437	1.35	163313	1.80
Totals	199249116	100.00	9055671	100.00



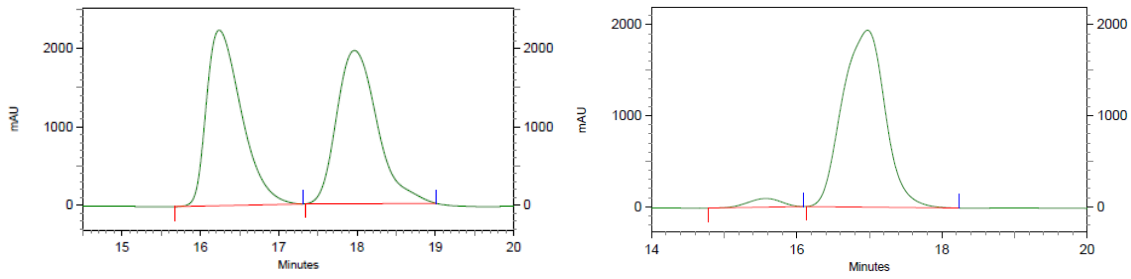
(*S*)-3-((4-Methoxybenzyl)oxy)-2-methylpropanal. (Table 3.2, 3.44). *Representative Procedure B* was used with olefin **3.43** (8.0 g, 45 mmol), $Rh(acac)(CO)_2$ (4.6 mg, 0.018 mmol), (*S,S*)-Ph-BPE (17.4 mg, 0.022 mmol) and toluene (5.1 mL). Reaction was stopped after 12 h with 95% conversion (b:l = 5.6:1, 93% *e.e.*) $[\alpha]_D^{21}$ = +28.886 (*c* = 0.72, $CHCl_3$, *l* = 50 mm). All spectrum data are in accordance with literature report.[49]

Analysis of Stereochemistry:

The titled compound **3.44** was reduced to the corresponding *p*-methoxybenzyl ether as shown below. The resulting benzyl ether was compared to racemic material prepared from 2-methyl-1,3-propanediol as shown below. Absolute stereochemistry was assigned by comparing optical rotation to literature $[\alpha]_D^{22}$ = +30.5 (*c* = 1.00, $CHCl_3$).[49]

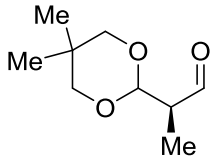


Chiral HPLC (Chiralpak, AD-H, 25 °C, 3 mL/min, 5% Isopropanol in hexane, 220 nm) – analysis of benzyl ether.



VWD: Signal A, 220 nm Results

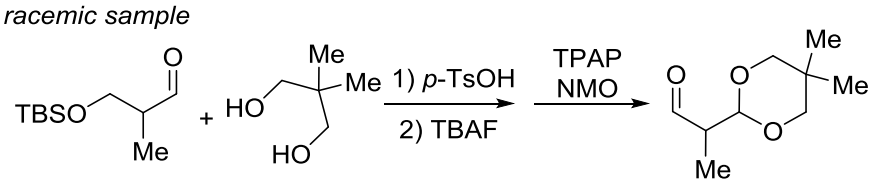
Retention Time	Area	Area %	Height	Height %
15.573	50852879	3.68	1602594	4.69
16.977	1332416422	96.32	32587530	95.31
Totals	1383269301	100.00	34190124	100.00



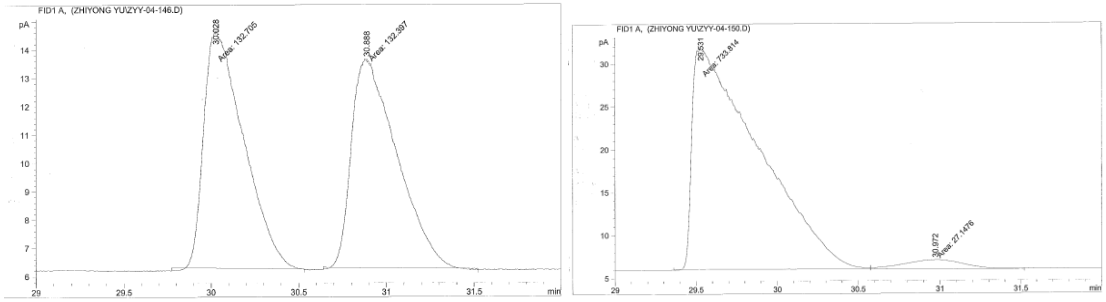
(*R*)-2-(5,5-Dimethyl-1,3-dioxan-2-yl)propanal (Table 3.2, 3.46). *Representative Procedure B* was applied with olefin **3.45** (2.0 g, 7.4 mmol), $Rh(acac)(CO)_2$ (1.5 mg, 0.014 mmol), (*S,S*)-Ph-BPE (5.4 mg, 0.017 mmol) and toluene (1.6 mL). Reaction was stopped after 12 h with full conversion (b:l = 12:1, 93% *e.e.*). $[\alpha]_D^{21}$ = +53.630 (*c* = 0.88, $CHCl_3$, *l* = 50 mm). All spectrum data are in accordance with literature report.[50]

Analysis of Stereochemistry:

The titled compound **3.46** was compared to racemic material. Absolute stereochemistry was assigned by analogy.

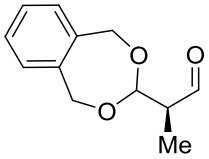


*Chiral GC (β-dex, supelco, 100 °C, 20 psi)-analysis of **3.46**.*



[50] Tanaka, K.; Fujimori, Y.; Saikawa, Y; Nakata, M. *J. Org. Chem.* **2008**, *73*, 6292.

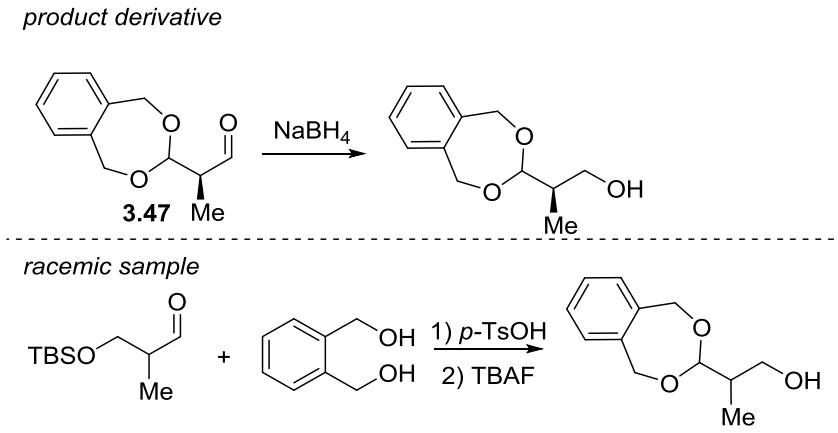
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	29.531	MF	0.4738	733.81372	25.81345	96.43245
2	30.972	FM	0.4149	27.14764	1.09051	3.56755



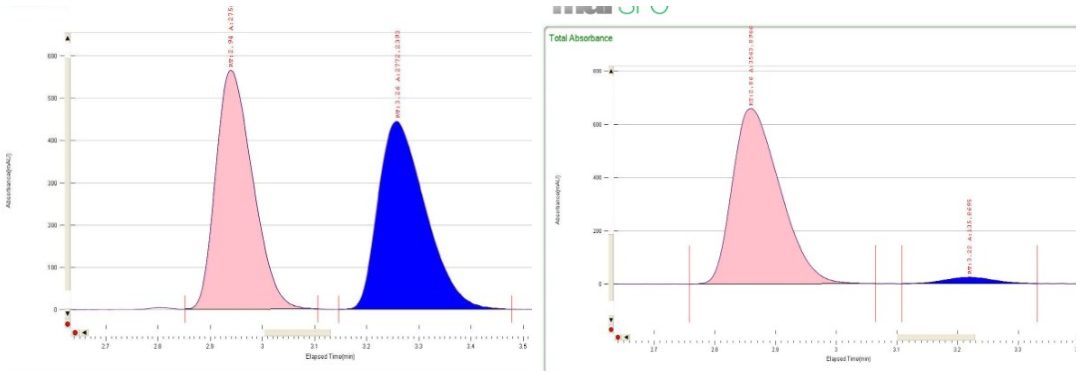
(*R*)-2-(1,5-Dihydrobenzo[e][1,3]dioxepin-3-yl)propanal. (Table 3.2, 3.48). *Representative Procedure B* was applied with olefin **3.47** (3.3 g, 18.8 mmol), $Rh(acac)(CO)_2$ (1.94 mg, 7.52 μmol), (*S,S*)-Ph-BPE (7.26 mg, 9.02 μmol) and toluene (4.3 mL). The reaction was stopped after 12 h with full conversion. (93% *e.e*., b:l = 13:1). The aldehyde was obtained as light yellow solid after concentration. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (1H, d, *J* = 2,0 Hz), 7.28-7.21 (4H, m), 5.09 (1H, d, *J* = 6.0 Hz), 4.97 (1H, d, *J* = 14.5 Hz), 4.96 (1H, d, *J* = 14.5 Hz), 4.92 (1H, d, 1H, d, *J* = 14.0 Hz), 4.90 (1H, d, *J* = 14.5 Hz), 2.79 (1H, qdd, *J* = 7.0, 7.0, 2.0 Hz),, 1.18 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.7, 139.21, 139.20, 128.1, 127.9, 109.1, 73.5, 73.0, 51.3, 9.7; IR (neat): 2960 (w), 2848 (w), 1724 (s), 1454 (m), 1373 (m), 1101 (s), 1043 (s), 1030 (s), 773 (m), 738 (s); HRMS-(ESI+) for $C_{12}H_{18}NO_3$ $[M+NH_4]^+$: calculated: 224.1287, found: 224.1278. $[\alpha]_D^{21}$ = +46.492 (*c* = 0.90, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The titled compound **3.48** was converted to the corresponding alcohol as shown below. The resulting alcohol was compared to racemic material prepared from racemic aldehyde as shown below. Absolute stereochemistry was assigned by analogy.

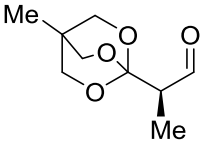


Chiral SFC (Chiralpak, AS-H, 35 °C, 5 mL/min, 5% Isopropanol, 100 bar, 210-270 nm) – analysis of alcohol.



Peak Info			
Peak No	% Area	Area	RT (min)
1	49.8582	2756.5624	2.94
2	50.1418	2772.2393	3.26
Total:	100	5528.8017	

Peak Info			
Peak No	% Area	Area	RT (min)
1	96.3276	3563.8966	2.86
2	3.6724	135.8695	3.22
Total:	100	3699.7661	

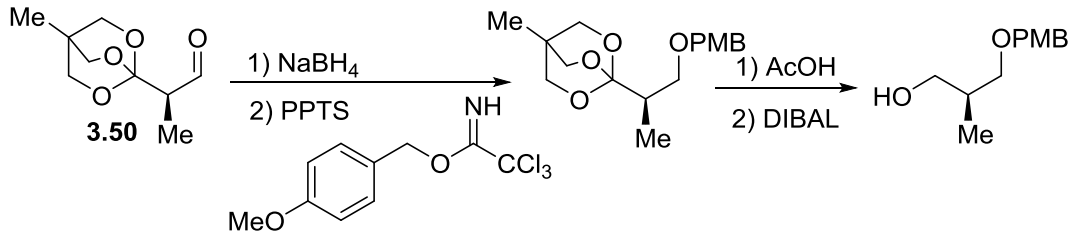


(*R*)-2-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)propanal (Table 3.2, 3.50). *Representative Procedure B* was applied with olefin **3.49** (1.6 g, 10.3 mmol), $Rh(acac)(CO)_2$ (2.0 mg, 0.082 mmol), (*S,S*)-Ph-BPE (8.0 mg, 0.098 mmol) and toluene (1.0 mL). Reaction reached full conversion after 5 h (b:l > 15:1, 89% *e.e.*). $[\alpha]_D^{21}$ = +65.933 (*c* = 0.72, $CHCl_3$, *l* = 50 mm). All spectrum data are in accordance with literature report.[21b]

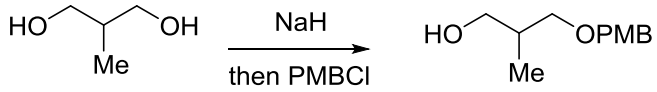
Analysis of Stereochemistry:

The titled compound **3.50** was converted to corresponding *p*-methoxybenzyl ether as shown below. The resulting benzyl ether was compared to racemic material prepared from 2-methyl-1,3-propanediol as shown below.

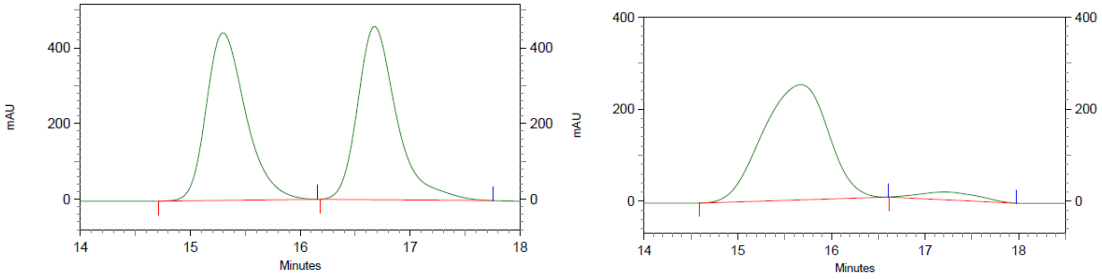
product derivative



racemic sample

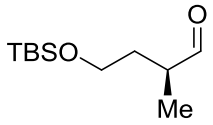


Chiral HPLC (Chiralpak, AD-H, 25 °C, 1 mL/min, 5% Isopropanol in hexane, 220 nm) – analysis of benzyl ether.



VWD: Signal A, 220 nm Results

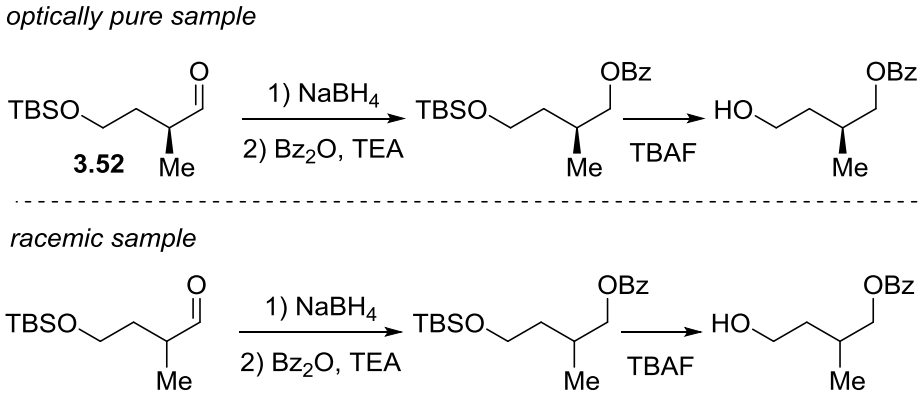
Retention Time	Area	Area %	Height	Height %
15.673	203707854	94.27	4201524	93.65
17.203	12373743	5.73	284950	6.35
Totals	216081597	100.00	4486474	100.00



(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylbutanal (Table 3.3, 3.52). The titled compound was prepared with *Representative Procedure A* on a 1.0 mmol scale with olefin **3.51**. Reaction reached full conversion after 5 h (b:l = 2:1, 95% *e.e.*). The crude reaction mixture was purified on silica gel (20:1 hexane:diethyl ether) to afford a clear, colorless oil. $[\alpha]^{22}_{D} = +18.347$ (*c* = 1.0, $CHCl_3$. *l* = 50 mm). All spectrum data are in accordance with literature.[51]

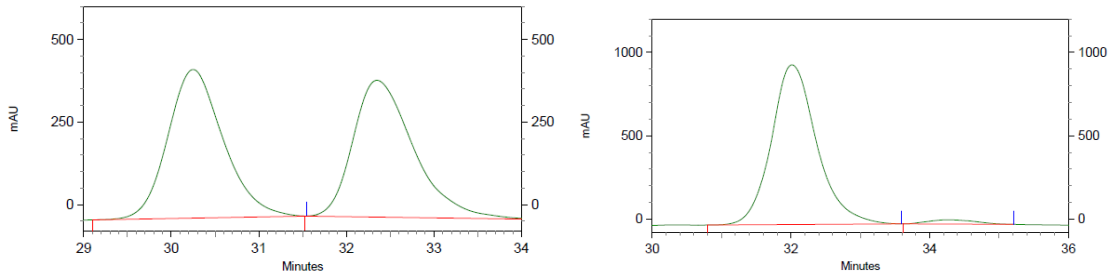
Analysis of Stereochemistry:

The titled compound **3.52** was subjected to $NaBH_4$ reduction followed by benzoate protection and TBS removal, as depicted below. The analogous racemic material was prepared by employing PPh_3 as ligand in hydroformylation of olefin **3.51**. Optical purity was determined by chiral HPLC analysis of the derived alcohol. Absolute stereochemistry was determined by analogy the optical rotation reported in the literature.[51]



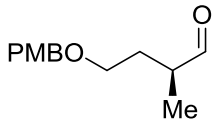
[51] (a) Fürst, R.; Rinner, U. *J. Org. Chem*. **2013**, *78*, 8748. (b) Enders, D.; Vicario, J. L.; Job, A.; Wolberg, M.; Müller, M. *Chem. Eur. J*. **2002**, *8*, 4272.

Chiral HPLC (Chiralpak, AD-H, 25 °C, 1 mL/min, 3 % Isopropanol in hexane, 220 nm) – analysis of alcohol.



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
32.013	730462339	97.33	16051857	97.44
34.263	20002090	2.67	422068	2.56
Totals	750464429	100.00	16473925	100.00



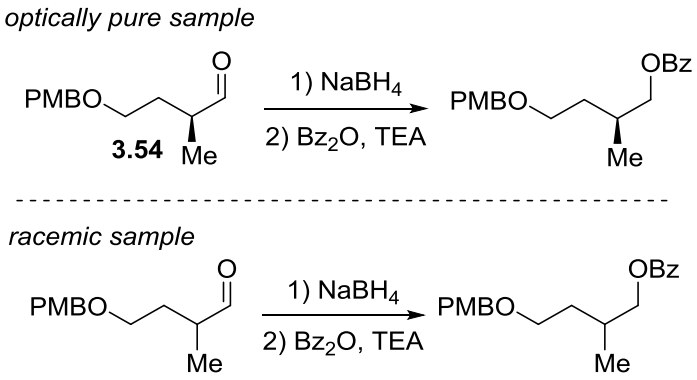
(*S*)-4-((4-Methoxybenzyl)oxy)-2-methylbutanal (Table 3.3, 3.54): The titled compound was prepared with *Representative Procedure A* on a 1.0 mmol scale with olefin **3.53**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil. R_f=0.17 (5:1 pentane: diethyl ether, stain $KMnO_4$). $[\alpha]^{22}_D$ = +15.453 (*c* = +0.522, $CHCl_3$, *l* = 50 mm). All spectral data are in accordance with the literature.[52]

Analysis of Stereochemistry:

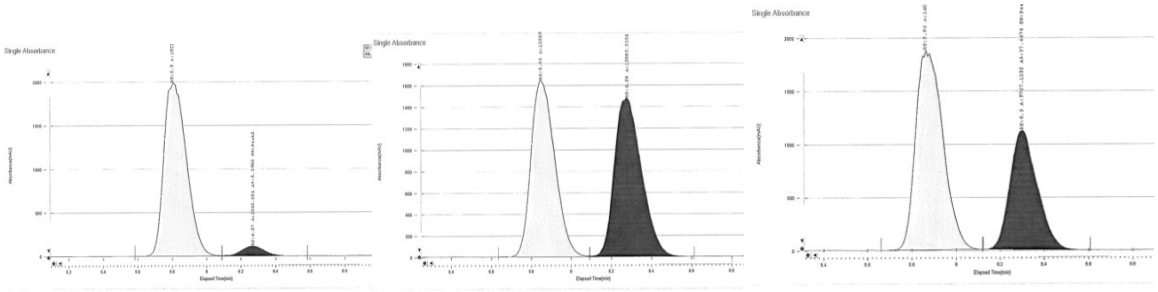
The title compound **3.54** was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound as compared to racemic

[52] Takagi, R.; Tsuyumine, S.; Nishitani, H.; Miyanaga, W.; Ohkata, K. *Aust. J. Chem.* **2004**, *57*, 439.

product. Absolute stereochemistry was determined by comparing to the optical rotation reported in the literature.[53]

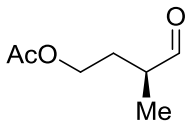


Chiral SFC (OD-H, Chiralpak, 215nm, 3.0 mL/min, 10% i-PrOH, 100 bar, 35°C)-analysis of benzoate protected compound.



Enatnioenriched Sample *Racemic Sample* *Co-injection*

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	94.6018	18227.1122	5.8	1988.7641	0.008
2	5.3982	1040.081	6.27	114.1512	0.0087
Total:	100	19267.1932			



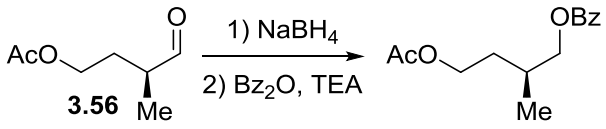
(*S*)-4-Acetoxy-2-methyl butanal (Table 3.3, 3.56): The title compound **3.56** was prepared with *Representative Procedure A* on a 1.0 mmol scale with olefin **3.55**. The crude reaction mixture was purified on silica gel (7:1 pentane: diethyl ether) to afford a clear, colorless oil. R_f = 0.26 (7:1 pentane: diethyl ether, stain in $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$): δ 9.63 (1H, d, J = 1.5 Hz), 4.14-4.11 (2H, m),

[53] Chen, J. L.-Y.; Brimble, M. A. *J. Org. Chem.* **2011**, *76*, 9417.

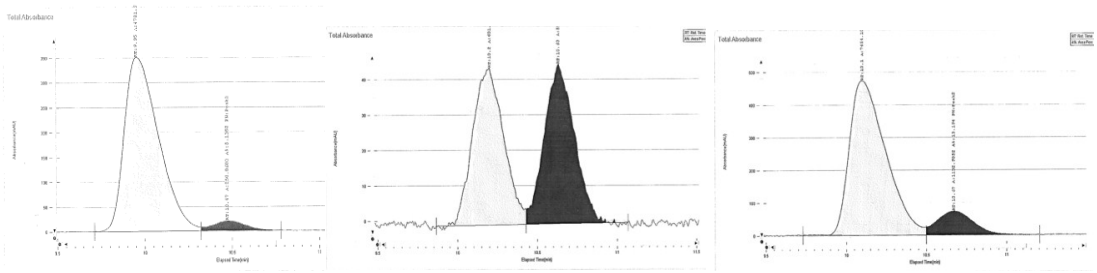
2.48 (1H, ddd, J = 14.0 Hz, 7.0 Hz, 7.0 Hz), 2.11-2.04 (1H, m), 2.02 (3H, m), 1.73-1.66 (1H, m) 1.14 (3H, dd, J = 7.5 Hz, 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.7, 170.9, 61.8, 43.5, 29.3, 20.8, 13.2; IR (neat): 2968 (w), 2932 (w), 1737 (s), 1459 (w), 1388 (w), 1367 (w), 1237 (s), 1052 (w) cm^{-1}; HRMS-(ESI+) for $C_7H_{12}O_3$ $[M+NH_4]^+$: calculated: 162.1130, found 162.1134. $[\alpha]^{22}_D$ = +2.245 (c = 0.481, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

The title compound **3.56** was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound as compared to racemic product. Absolute stereochemistry was determined by analogy.

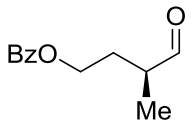


Chiral SFC (OD-H, Chiralpak, 215nm, 3.0 mL/min, 1% i-PrOH, 100 bar, 35°C)-analysis of benzoate.



Enantioenriched Sample *Racemic Sample* *Co-injection*

Peak Info					
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	94.8648	4781.9996	9.95	350.1341	0.0088
2	5.1352	258.8603	10.47	19.8137	0.0093
Total:	100	5040.8599			

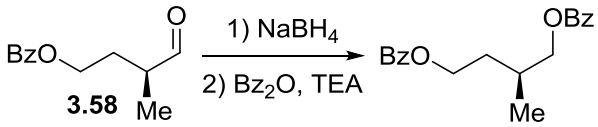


(*S*)-3-Methyl-4-oxobutyl benzoate (Table 3.3, 3.58): The title compound **3.58** was prepared with *Representative Procedure A* on a 1.0 mmol scale with olefin **3.57**. The crude reaction mixture was purified on silica gel (3:1 pentane: diethyl ether) to afford a clear, colorless oil. R_f = 0.19 (3:1 pentane: diethyl ether, stain in 2,4-DNP). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.71 (1H, d, *J* = 1.5 Hz), 8.10-8.00 (2H, m), 7.56 (1H, dddd (app tt), *J* = 7.5 Hz, 7.5 Hz, 1.5 Hz, 1.5 Hz), 7.44 (2H, dd (app t), *J* = 8.0 Hz, 8.0 Hz), 4.44-4.37 (2H, m), 2.59 (1H, dddd (app tt), *J* = 7.0 Hz, 7.0 Hz, 7.0 Hz, 1.5 Hz), 2.25 (1H, dddd (app dq), *J* = 14.5 Hz, 6.5 Hz, 6.5 Hz, 6.5 Hz), 1.85 (1H, dddd (app dq), *J* = 14.5 Hz, 6.5 Hz, 6.5 Hz, 6.5 Hz), 1.21 (3H, d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 203.8, 166.4, 133.0, 129.6, 128.4, 62.4, 29.5, 13.3; IR (neat): 2968 (m), 2931 (m), 1717 (s), 1452 (m), 1272 (s), 1070 (m), 936 (w), 711 (m) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{15}O_3$ [M+H]: calculated: 207.1021, found 207.1015. $[\alpha]^{22}_D$ = +38.947 (*c* = 0.723, $CHCl_3$).

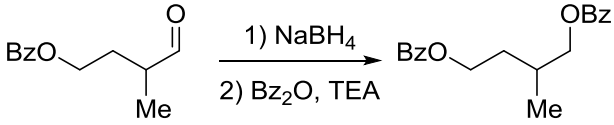
Analysis of Stereochemistry:

The title compound **3.58** was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound as compared to racemic product. Absolute stereochemistry was determined by analogy.

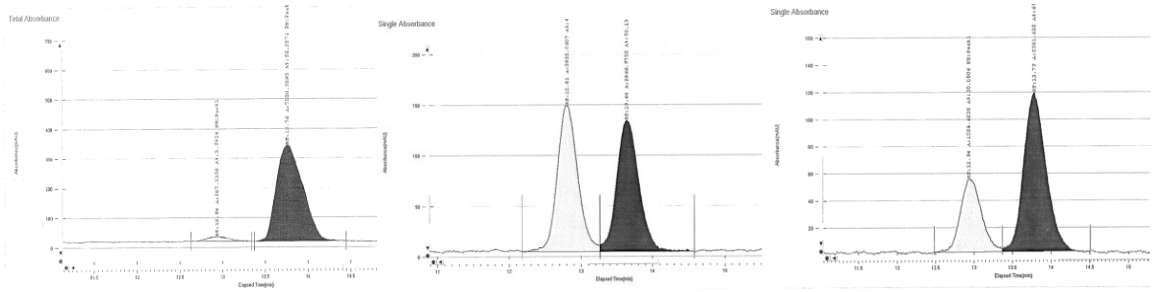
optically pure sample



racemic sample



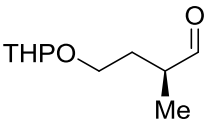
Chiral SFC (OJ-H, Chiralpak, 215nm, 3.0 mL/min, 2% i-PrOH, 100 bar, 35°C)-analysis of bis-benzoate.



Enatnioenriched Sample *Racemic Sample* *Co-injection*

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	3.9424	287.3358	12.94	15.8878	0.0199
2	96.0576	7000.9285	13.76	323.7626	0.0212
Total:	100	7288.2643			

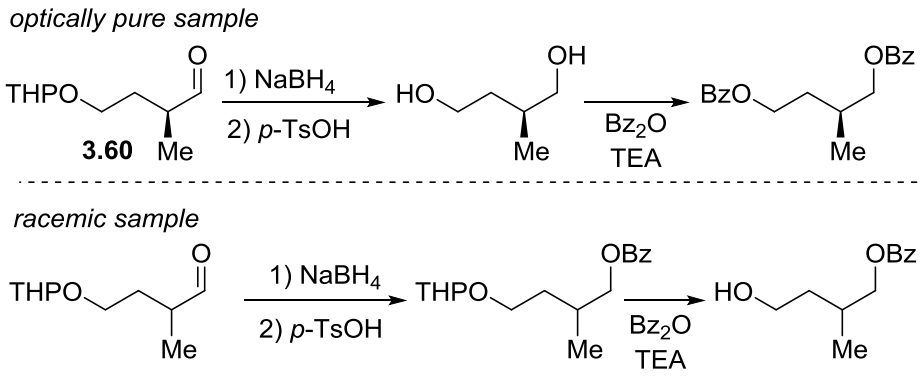


(2*S*)-2-Methyl-4-((tetrahydro-2*H*-pyran-2-yl)oxy)butanal (Table 3.3, 3.60): The title compound **3.60** was prepared with *Representative Procedure A* on a 1.0 mmol scale with 2-(but-3-en-1-yloxy)tetrahydro-2*H*-pyran **3.59** and obtained as 1:1 mixure of inseparable diasteromers. The crude reaction mixture was purified on silica gel (20:1 pentane: diethyl ether) to afford a clear, colorless oil. R_f= 0.17 (10:1 pentane: diethyl ether, stain in 2,4-DNP). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.65 (1H, d, *J* = 1.5 Hz), 9.64 (1H, d, *J* = 2.0 Hz), 4.56-4.55 (2H, m), 3.52-3.48 (2H, m), 3.43 (2H, dddd, *J* = 22.0 Hz, 12.5 Hz, 7.0 Hz, 6.0 Hz), 2.56-2.47 (2H, m), 2.03 (2H, ddt, *J* = 14.0

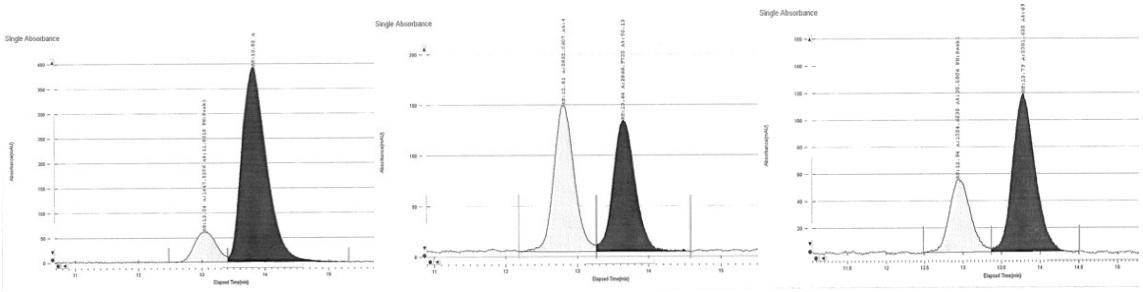
Hz, 7.5 Hz, 5.5 Hz), 1.80-1.66 (6H, m), 1.58-1.49 (8H, m), 1.13 (3H, d, J = 1.5 Hz), 1.12 (3H, d, J = 2.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.7, 98.9, 98.8, 64.8, 64.5, 62.2, 44.0, 43.8, 31.0, 30.8, 30.5, 25.4, 19.4, 13.3, 13.1; IR (neat): 2939 (m), 2872 (m), 2714 (w), 1723 (s), 1120 (m), 1022 (m), 973 (s), 732 (m), cm^{-1}; HRMS-(ESI+) for $C_{10}H_{19}O_3$ [M+H]: calculated: 187.1334, found 187.1344. $[\alpha]_D^{22}$ = +26.258 (c = 0.646, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

The title compound **3.60** was subjected to $NaBH_4$ reduction, followed by removal of the tetrahydropyranyl ether group and bis-benzoyl protection, as depicted below. The analogous racemic material was prepared *via* the same route, using tricylcohexylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound. Absolute stereochemistry was determined by analogy.

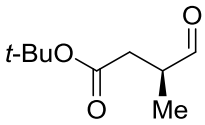


Chiral SFC (OJ-H, Chiralpak, 215nm, 3.0 mL/min, 2% i-PrOH, 100 bar, 35°C)-analysis of benzoate protected compound.



Enantioenriched Sample *Racemic Sample* *Co-injection*

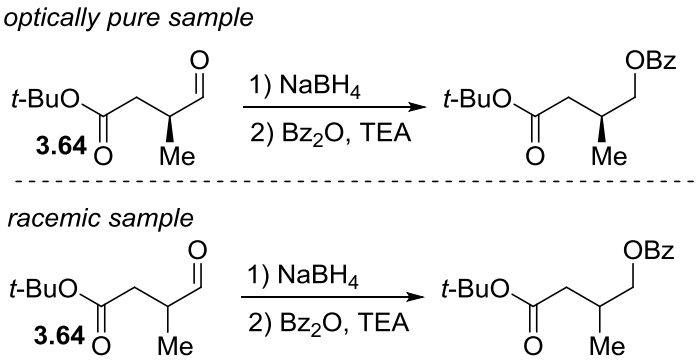
Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	11.8018	1447.5256	13.04	60.7848	0.0125
2	88.1982	10817.8139	13.82	393.3788	0.0133
Total:	100	12265.3395			



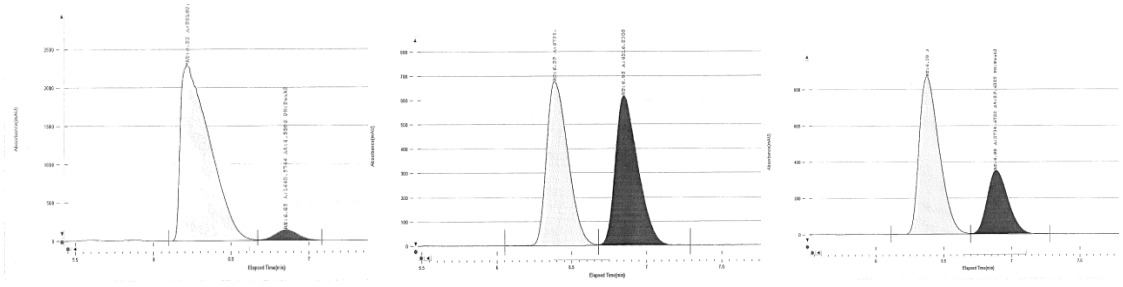
***tert*-Butyl-(S)-3-methyl-4-oxobutyl (Table 3.3, 3.64)**: The titled compound **3.64** was prepared with *Representative Procedure A* on a 1.0 mmol scale with but-3-enoic acid *tert*-butyl ester **3.63**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil. R_f = 0.12 (10:1 pentane: diethyl ether, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.69 (1H, d, J = 1.0 Hz), 2.78 (1H, ddd (app dq), J = 14.0 Hz, 14.0 Hz, 7.0 Hz), 2.64 (1H, dd, J = 16.0 Hz, 7.0 Hz), 2.34 (1H, dd, J = 16.5 Hz, 6.5 Hz), 1.44 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.9, 170.9, 81.0, 42.8, 36.4, 28.0, 13.2; IR (neat): 2978 (w), 2933 (w), 2717 (w), 1727 (s), 1367 (w), 1156 (w) cm^{-1}; HRMS-(ESI+) for $C_9H_{16}O_3$ [M+H]: calculated: 173.1178, found 173.1184. $[\alpha]^{22}_D$ = −98.065 (c = 0.153, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

The title compound **3.64** was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound as compared to racemic product. Absolute stereochemistry was determined by analogy.



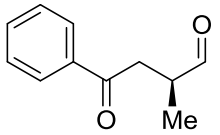
Chiral SFC (OD-H, Chiralpak, 215nm, 3.0 mL/min, 1% i-PrOH, 100 bar, 35°C)-analysis of benzoate protected compound.



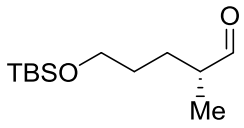
Enantioenriched Sample *Racemic Sample* *Co-injection*

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	95.4414	30160.4156	6.22	2319.5375	0.0057
2	4.5586	1440.5744	6.85	138.464	0.0062
Total:	100	31600.99			



(*S*)-2-Methyl-4-oxo-4-phenylbutanal (Table 3.3, 3.66). The titled compound was prepared with *Representative Procedure A* on a 1.0 mmol scale with olefin **3.65**. All spectral data are in accordance with the literature.[54]

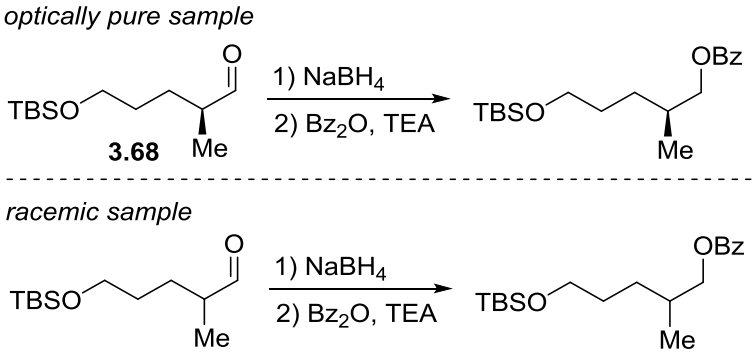


(*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-2-methylpentanal (Table, 3.3, 3.68): The titled compound was prepared with *Representative Procedure A* (but using (*R,R*)-Ph-BPE ligand) on a 1.0 mmol scale with (1,1-dimethylethyl)(dimethyl)(4-pentenyloxy)silane **3.67**. The crude reaction mixture was purified on silica gel (10:1 pentane: diethyl ether) to afford a clear, colorless oil. R_f = 0.26 (10:1 pentane: diethyl ether, stain in $KMnO_4$). $[\alpha]^{22}_D = -46.830$ (*c* = 0.556, *l* = 50 mm, $CHCl_3$). All spectral data were in accordance with the literature.[55]

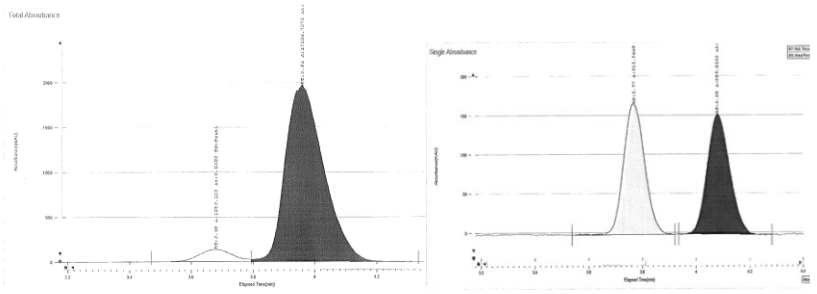
Analysis of Stereochemistry:

The titled compound **3.68** was subjected to $NaBH_4$ reduction followed by benzoate protection, as depicted below. The analogous racemic material was prepared *via* the same route, using triphenylphoshine as achiral ligand in the hydroformylation reaction. Optical purity was determined by SFC analysis of the derived compound as compared to racemic product. Absolute stereochemistry was determined by comparison with literature.[55]

[54] Zhang, J.; Xing, C.; Tiwari, B.; Chi, Y. *J. Am. Chem. Soc*. **2013**, *135*, 8113.
[55] Rentsch, A.; Kalesse, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 11381.



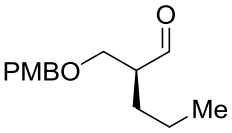
Chiral SFC (OD-H, Chiralpak, 215nm, 3.0 mL/min, 3% i-PrOH, 100 bar, 35°C)-analysis of benzoate.



Enantioenriched Sample *Racemic Sample*

Peak Info

Peak No	% Area	Area	RT (min)	Height (mV)	K'
1	5.8303	1059.123	3.68	138.5669	0.0067
2	94.1697	17106.7375	3.96	1972.3598	0.0072
Total:	100	18165.8605			

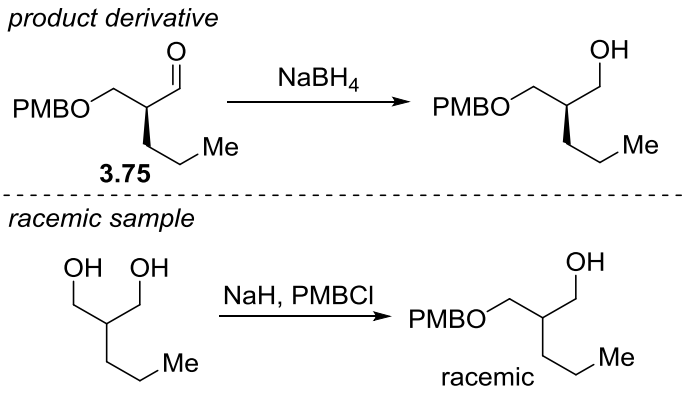


(*S*)-2-(((4-Methoxybenzyl)oxy)methyl)pentanal (Scheme 3.11, 3.75). *Representative Procedure B* was applied with olefin **3.74** (207 mg, 1.0 mmol), $Rh(acac)(CO)_2$ (2.6 mg, 0.01 mmol), (*S,S*)-Ph-BPE (8.0 mg, 0.012 mmol) and toluene (1.0 mL). Reaction reached full conversion after 5 h (b:l = 7.8:1, 81% *e.e.*). The crude reaction mixture was purified on silica gel (12:1 hexane: diethyl ether) to afford a clear, colorless oil. R_f = 0.35 (6:1 hexane:diethyl ether, stain in $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$): δ 9.68 (1H, d, *J* = 2.5 Hz), 7.23 (2H, d, *J* = 9.0 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 4.43 (2H, m), 3.80 (3H, s), 3.66 (1H, dd, *J* = 9.0 Hz, 7.0 Hz), 3.61 (1H, dd,

J = 9.5 Hz, 5.0 Hz), 2.55 (1H, m), 1.65 (1H, ddt, *J* = 14.5 Hz, 7.5 Hz, 7.5 Hz), 1.45 (1H, ddt, *J* = 14.5 Hz, 7.0 Hz, 7.0 Hz), 1.33 (2H, 2H, qt, *J* = 7.0 Hz, 7.0 Hz), 0.91 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 204.4, 159.5, 130.2, 129.4, 114.0, 73.1, 68.5, 55.5, 52.2, 28.2, 20.4, 14.3; IR (neat): 2958 (w), 2933 (w), 2864 (w), 1725 (s), 1612 (m), 1513 (s), 1465 (w), 1247 (s), 1086 (s), 1034 (s), 819 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{19}O_3$ [M+H]: calculated: 235.1334, found: 235.1343. $[\alpha]_D^{22}$ = −17.033 (c = 0.95, $CHCl_3$).

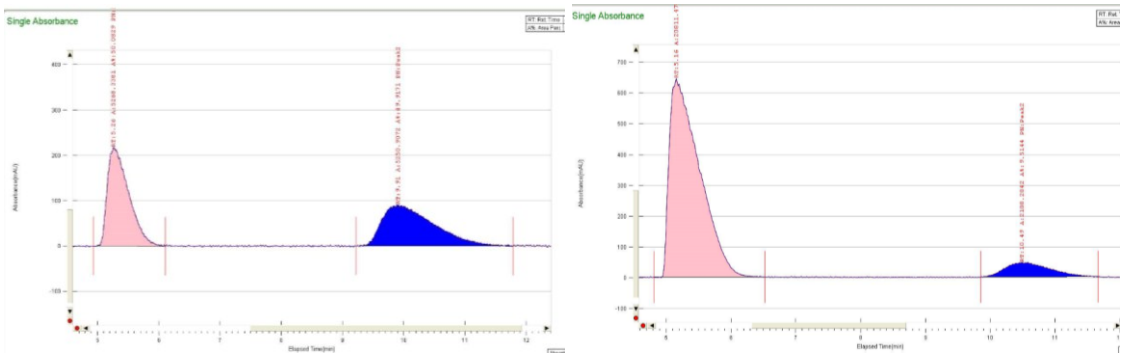
Analysis of Stereochemistry:

The titled compound **3.75** was converted to the corresponding alcohol as shown below. The resulting alcohol was compared to racemic material prepared from 2-propyl-propan-1,3-diol. Absolute stereochemistry was assigned by comparing optical rotation of the alcohol to literature [lit. $[\alpha]_D^{22}$ = −14.0 (*c* = 1.1, $CHCl_3$)].[56]



[56] Yadav, J. S.; Nanda, S. *Tetrahedron: Asymmetry*, **2001**, *12*, 3223.

Chiral SFC (AS-H, Chiralpak, 215nm, 3.0 mL/min, 15% i-PrOH, 100 bar, 35°C)-analysis of alcohol.



Peak Info

Peak Name	Number	Concentration	Area %	Area
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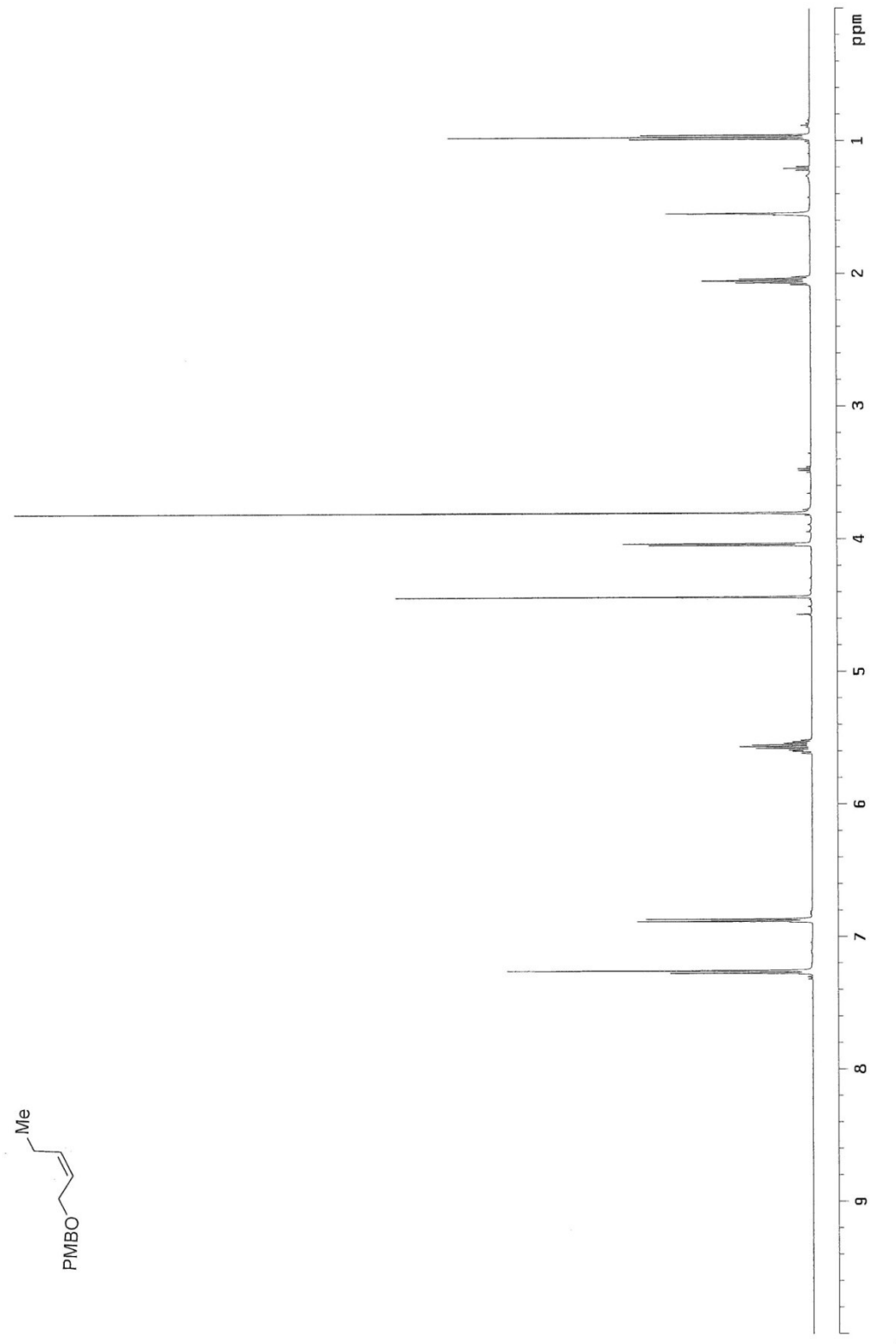
Peak2	2	0	9.5144	2188.2842

Area Sum	RT (min)	St. (min)	End (min)	Height	Width (min)
	5.16	4.8145	6.5227	644.6855	1.7099
22999.7591	10.49	9.8513	11.6601	46.2777	1.8104

3.6. Spectrum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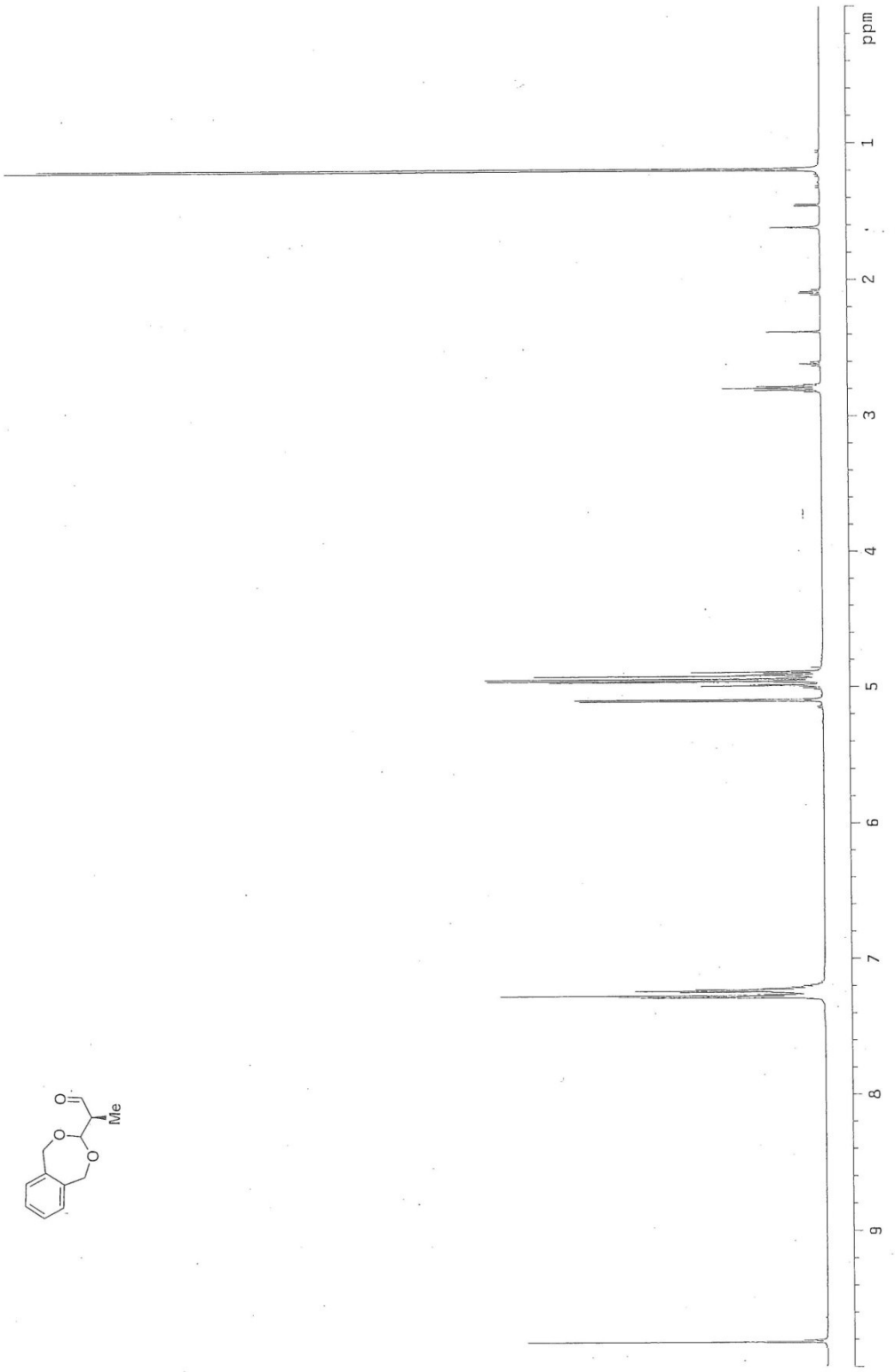
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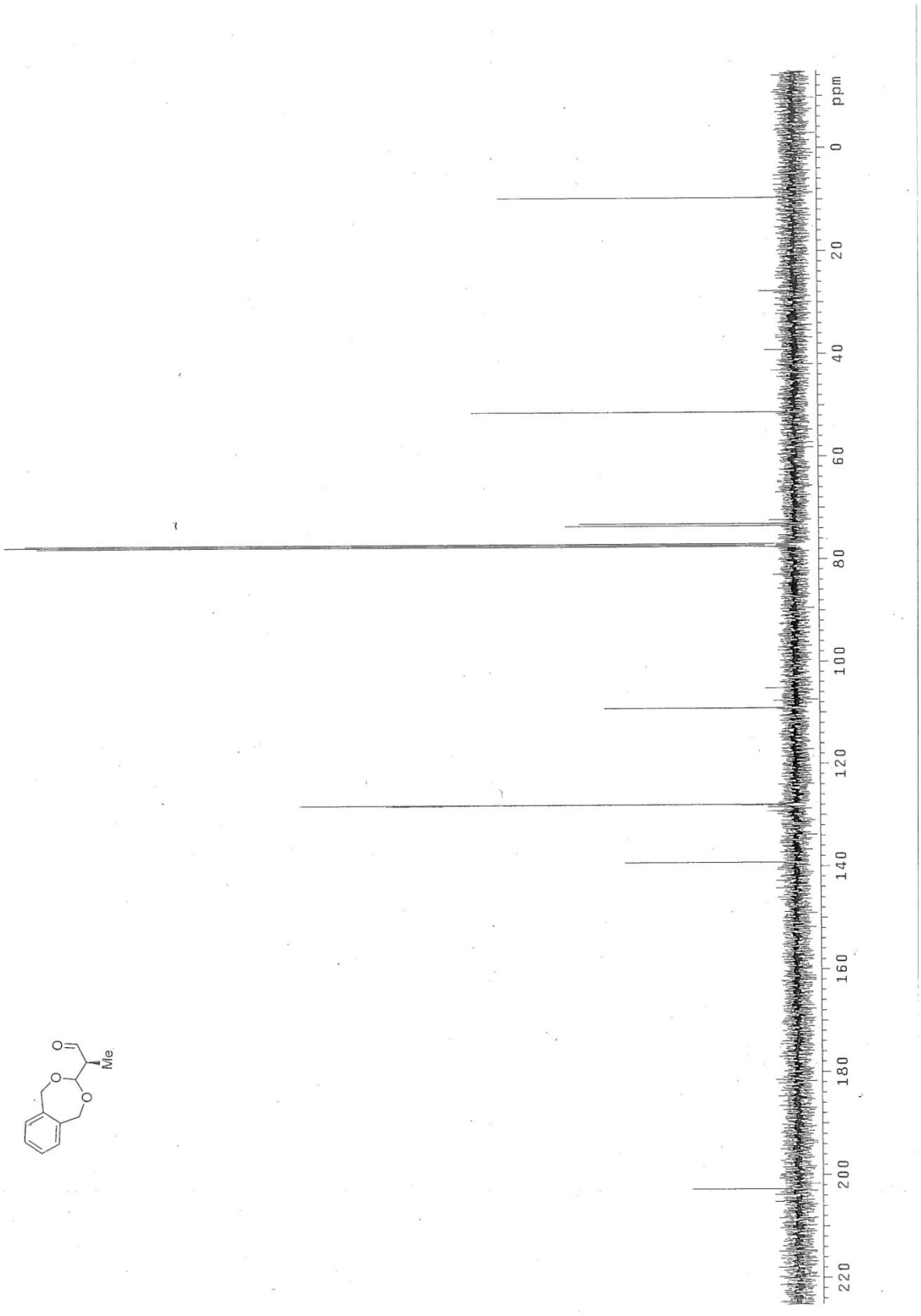
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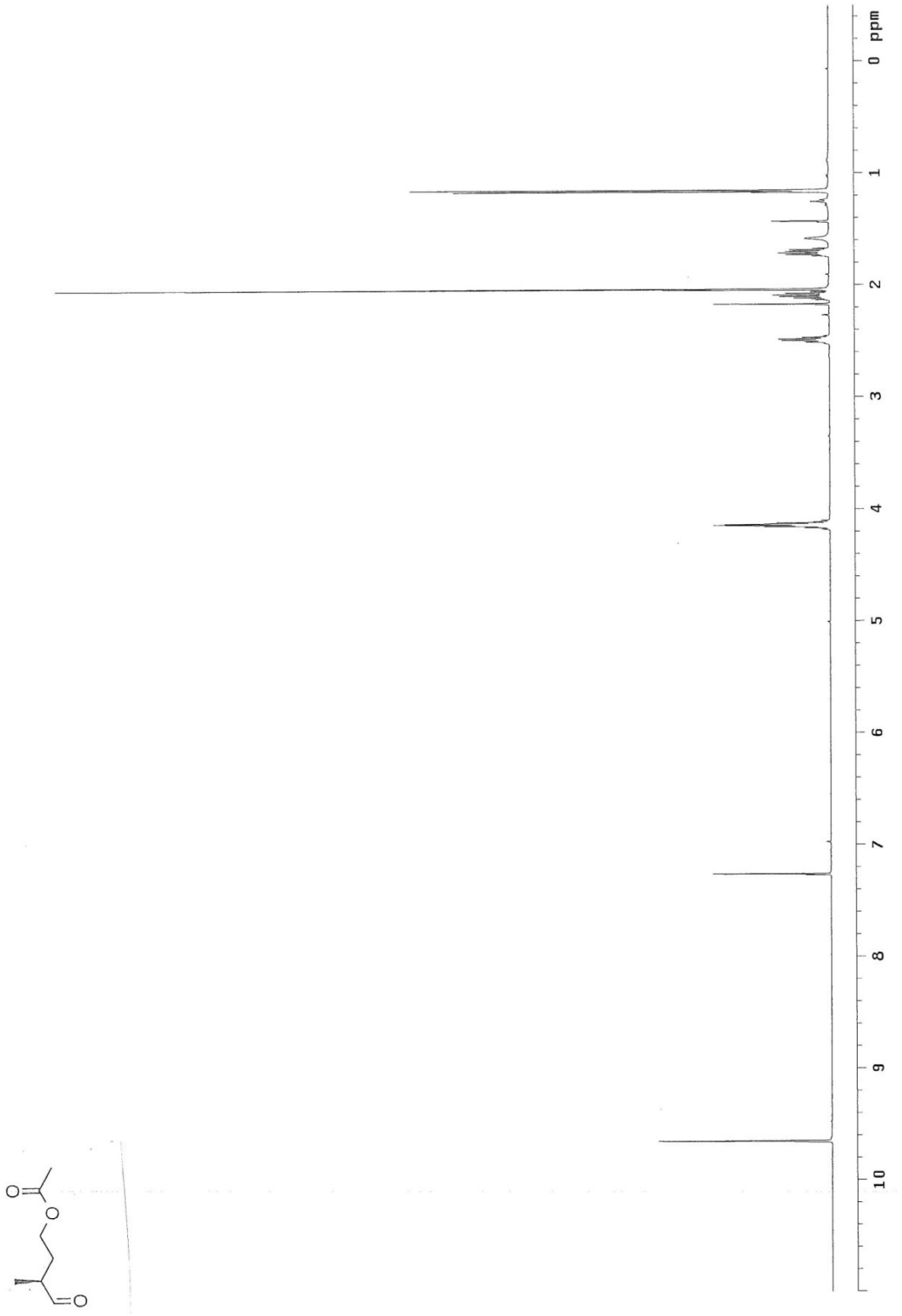
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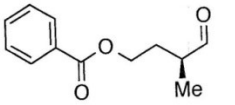
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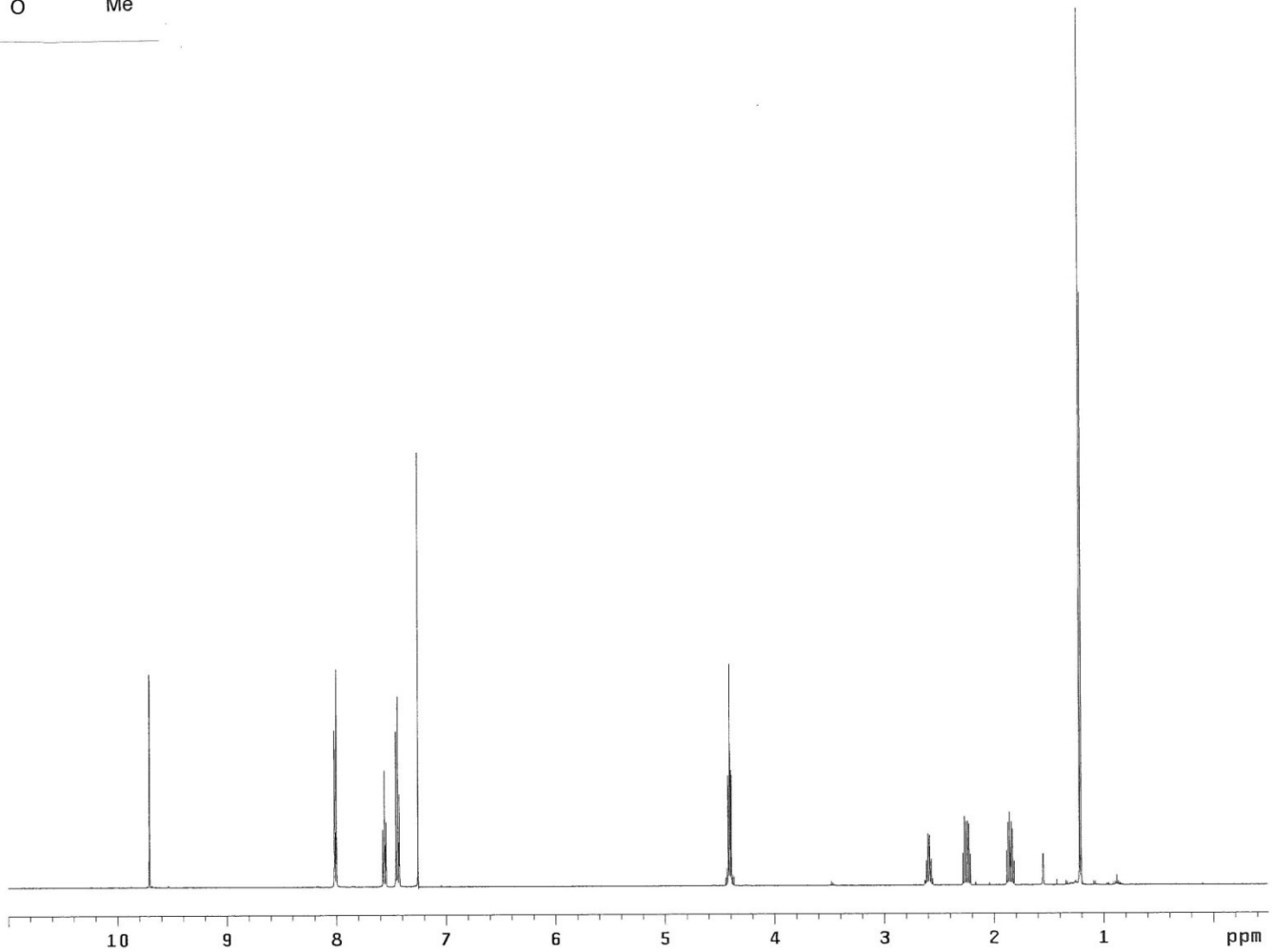
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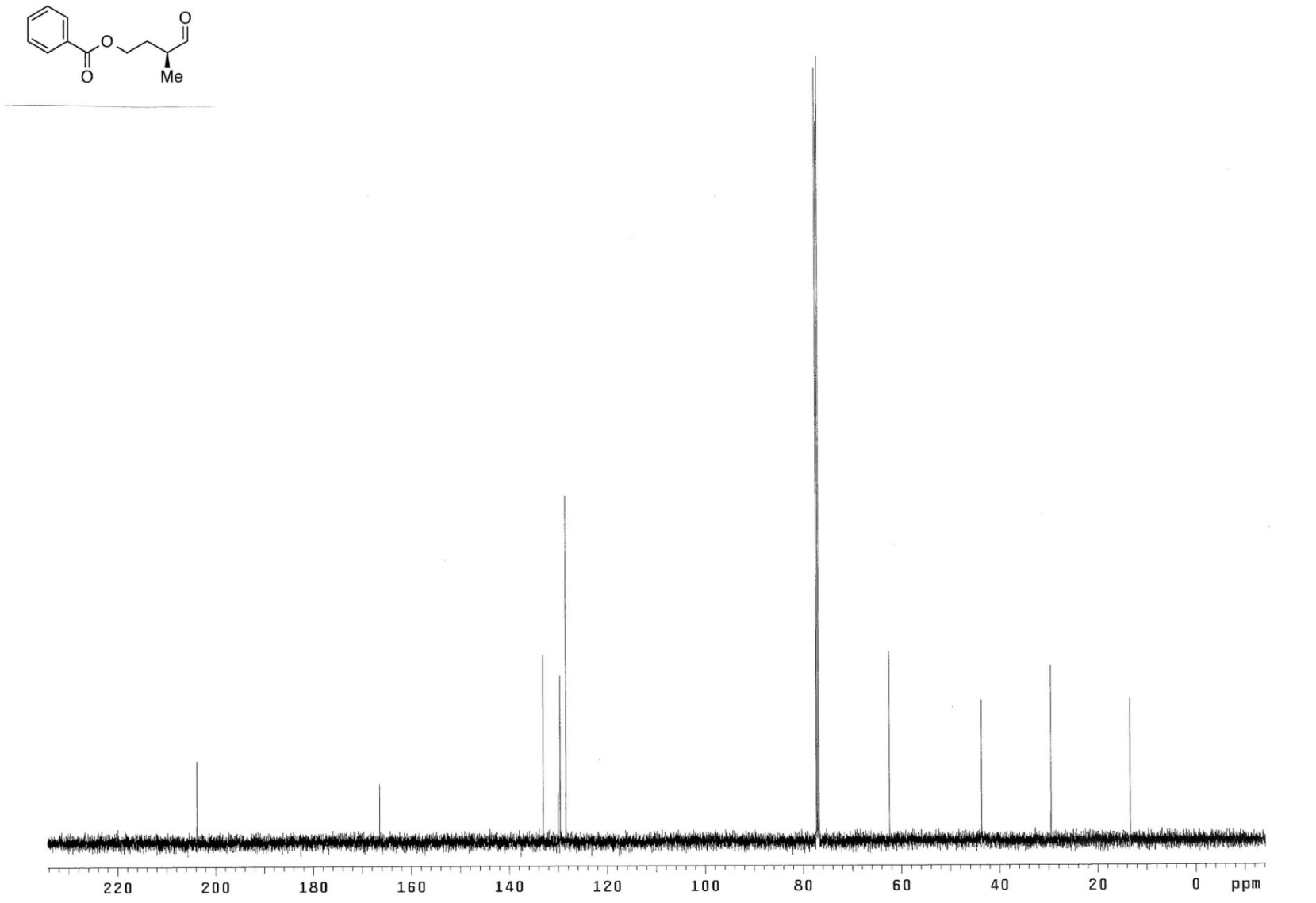
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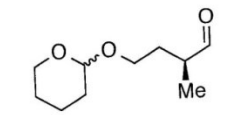
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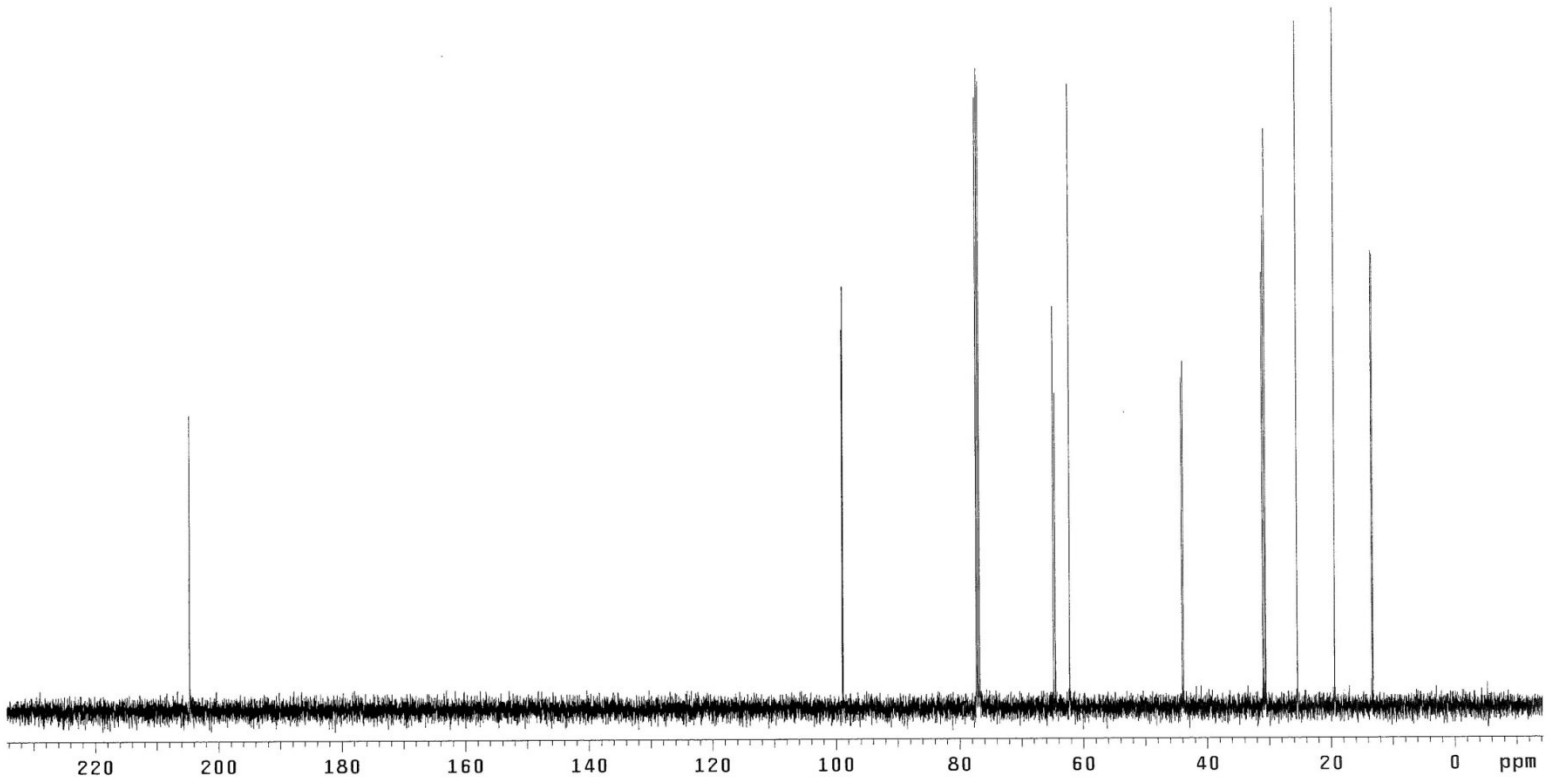
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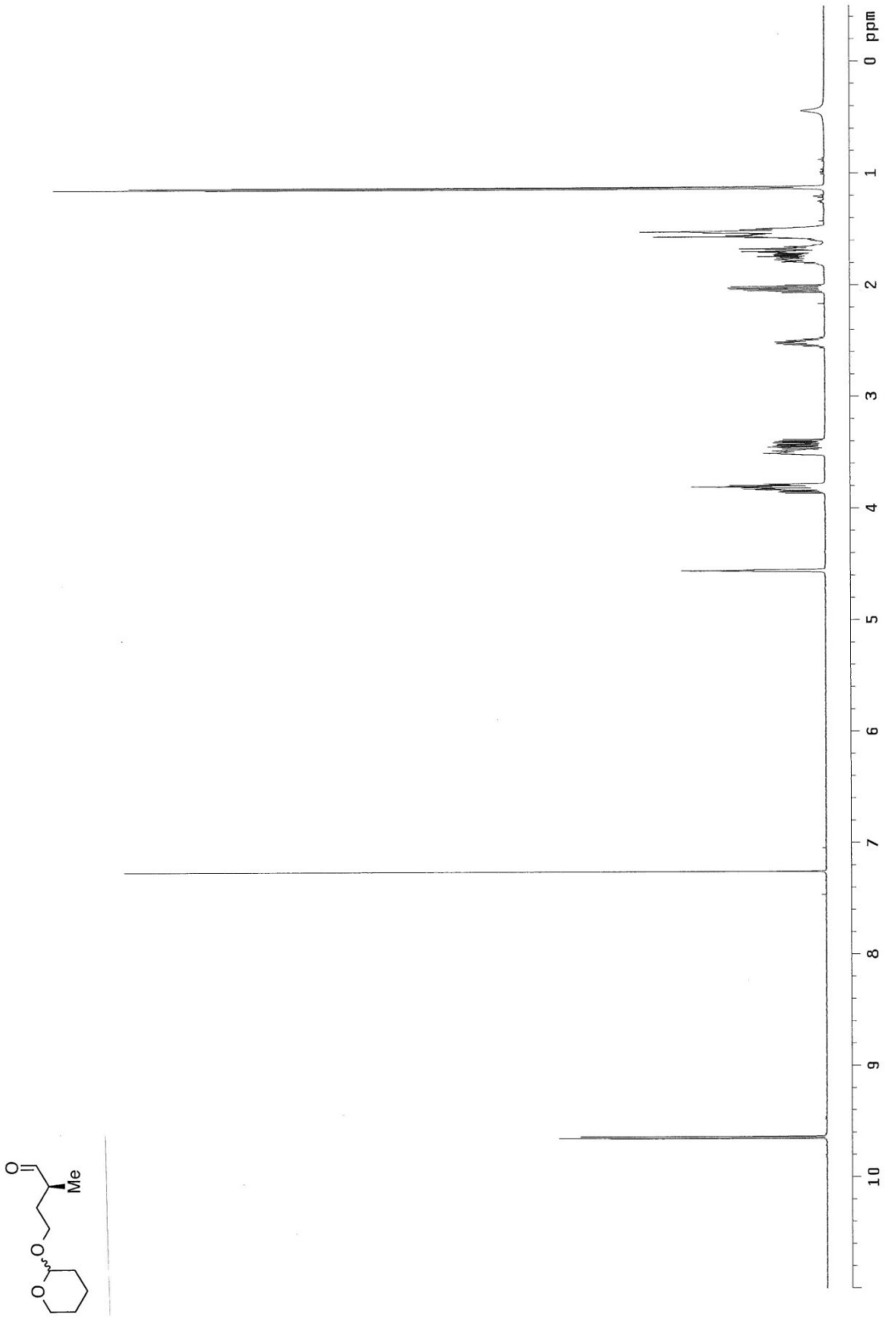
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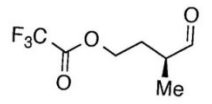
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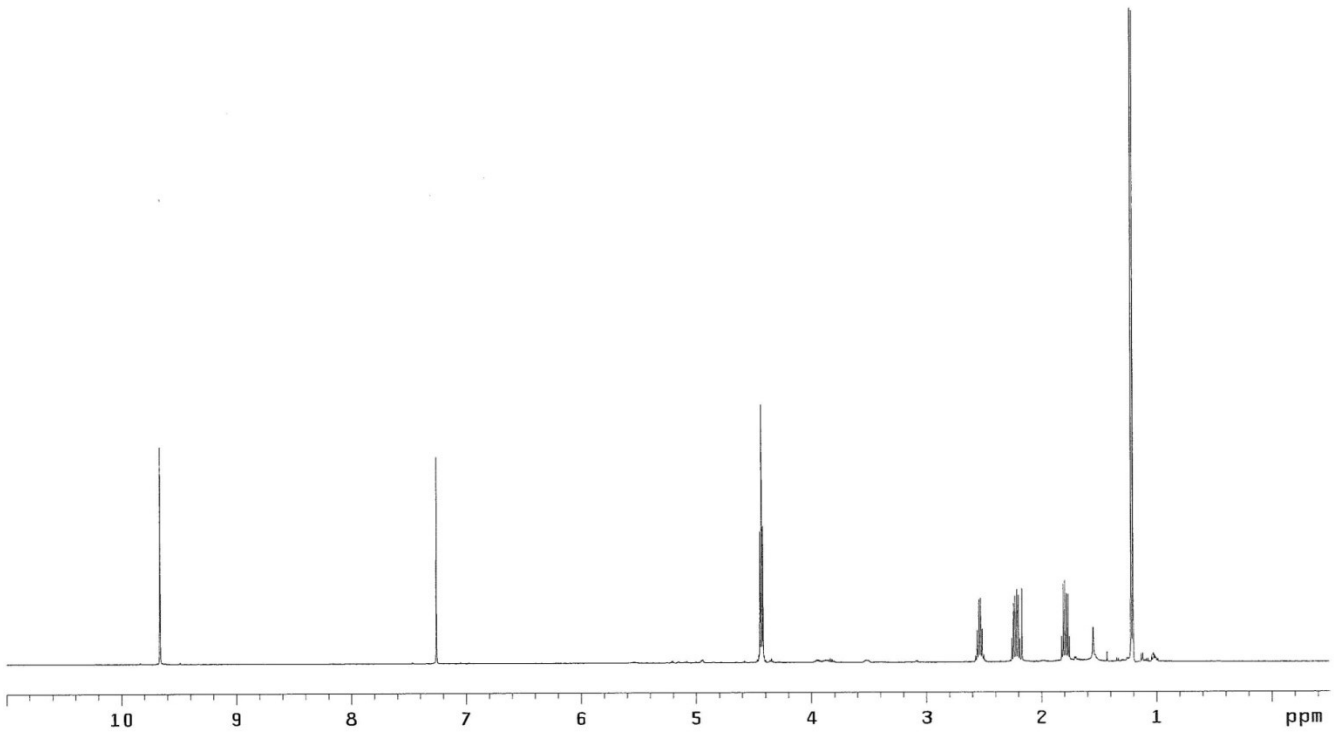
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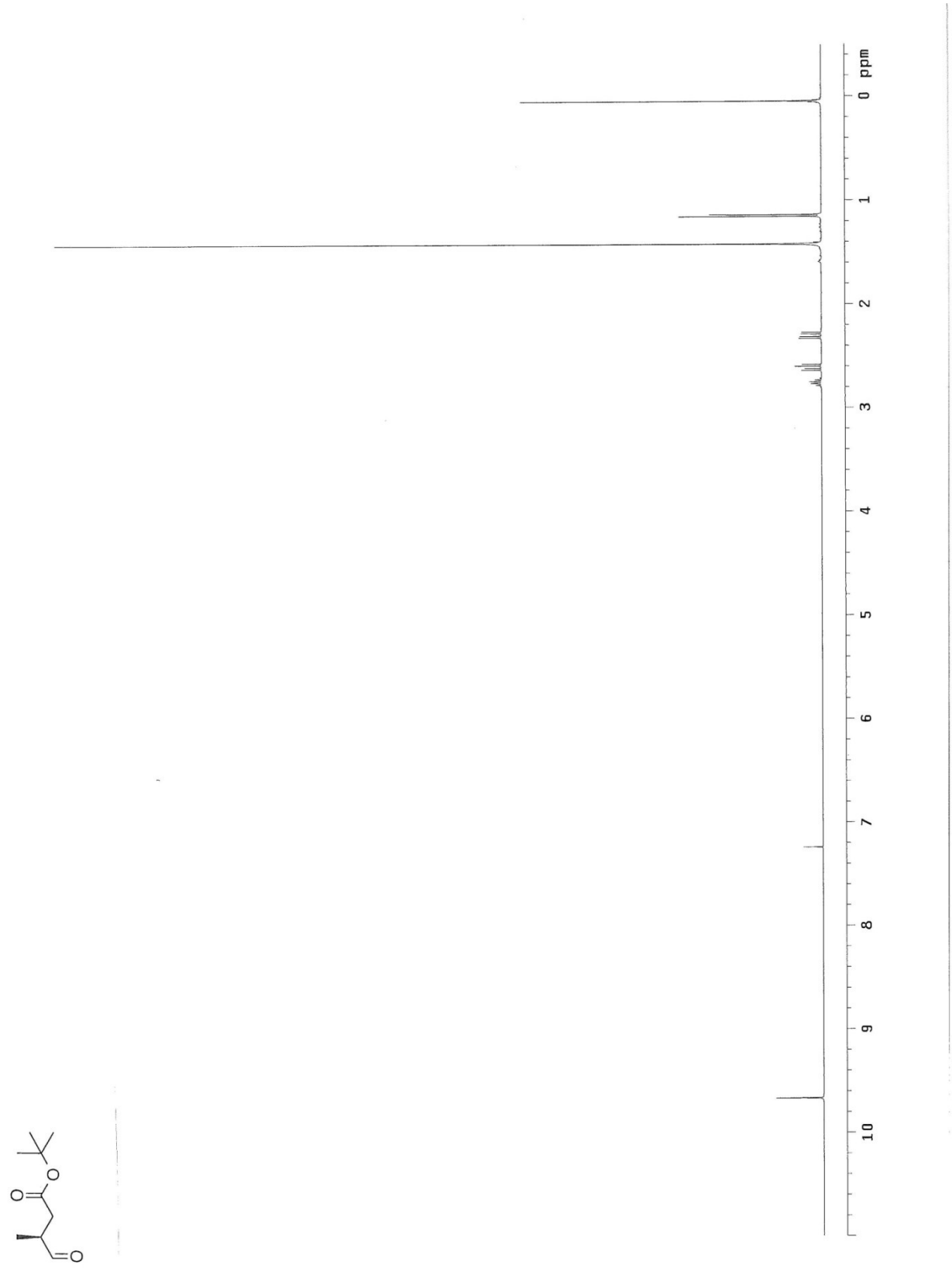
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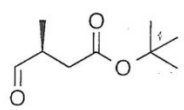

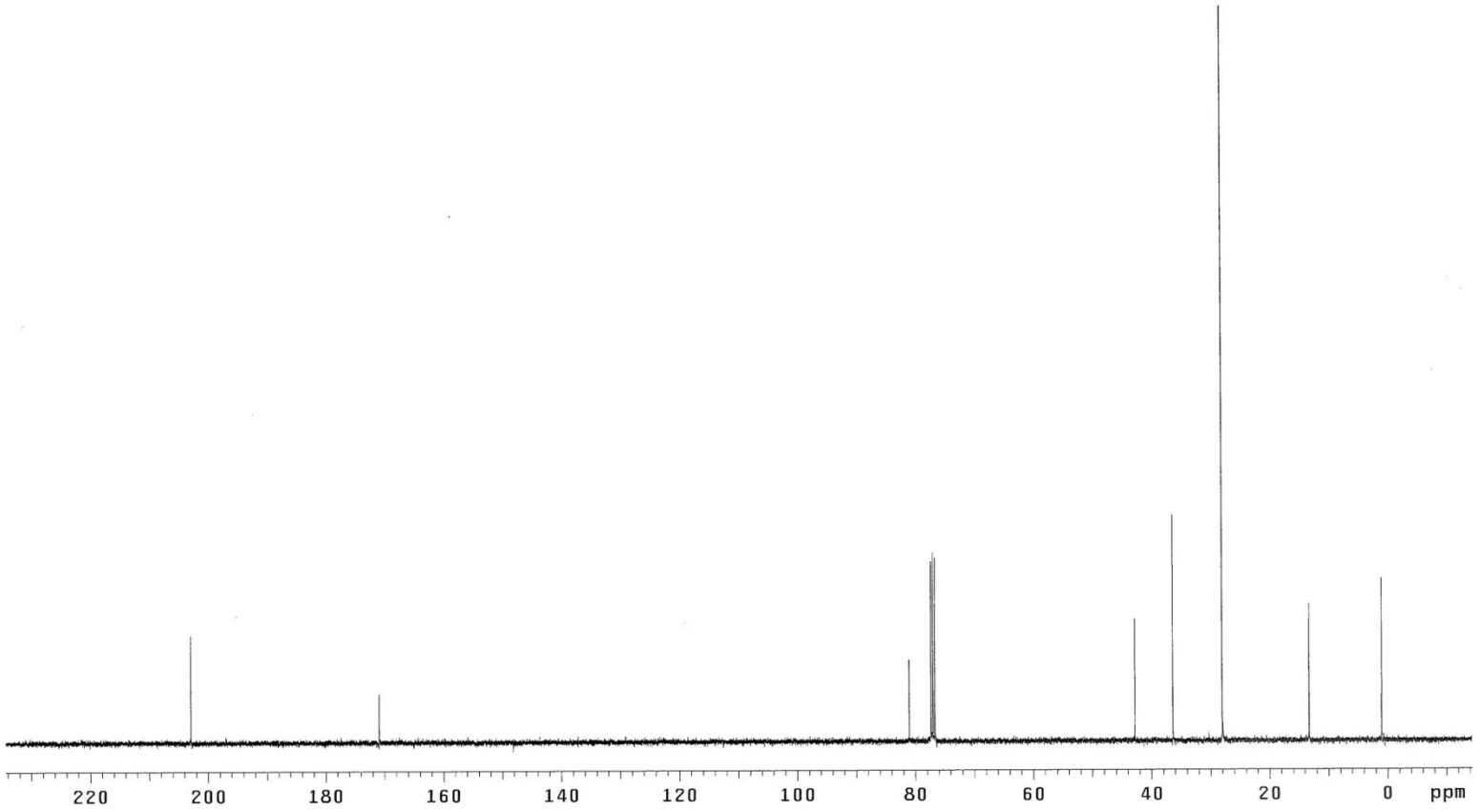
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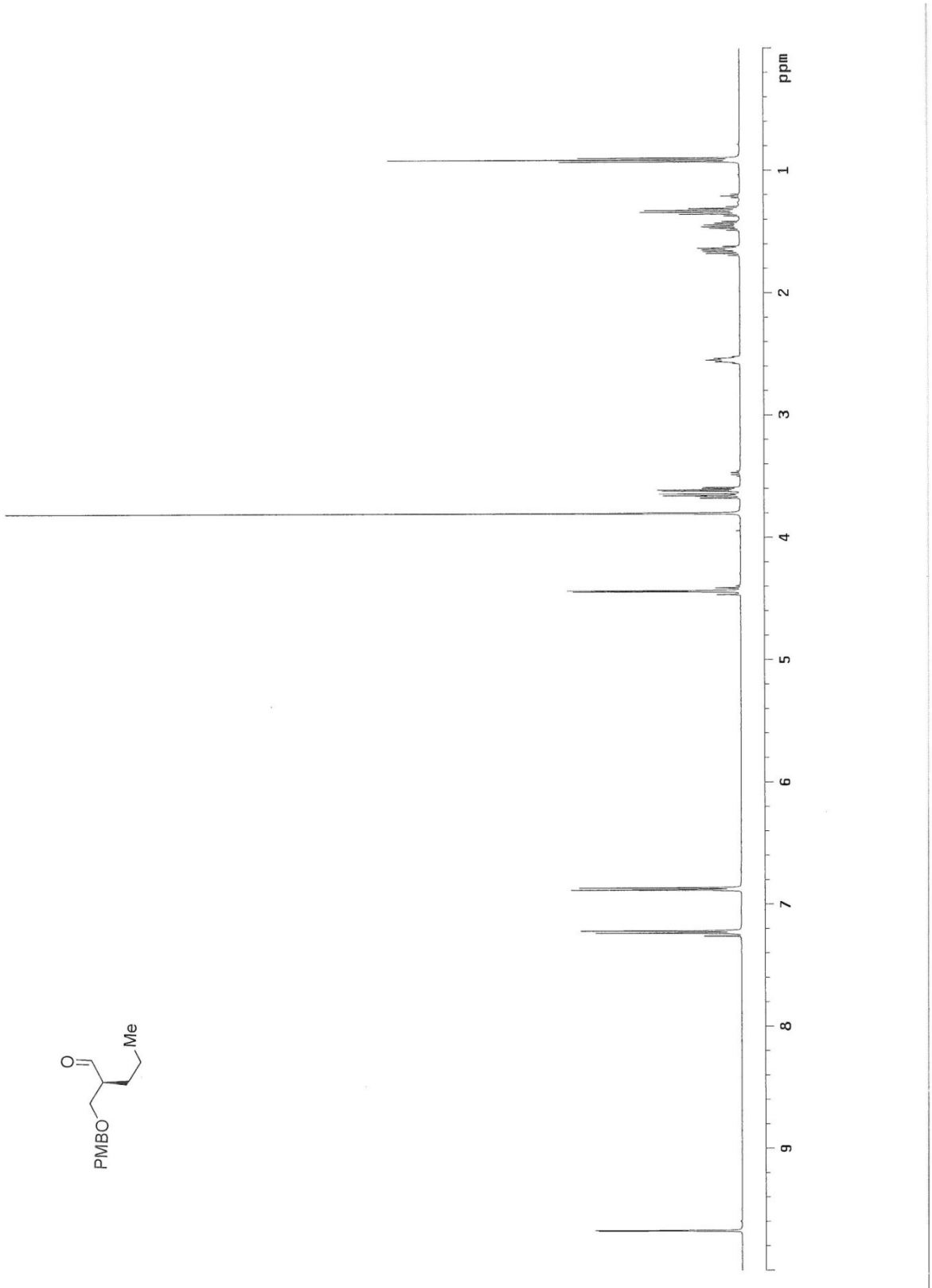
ppm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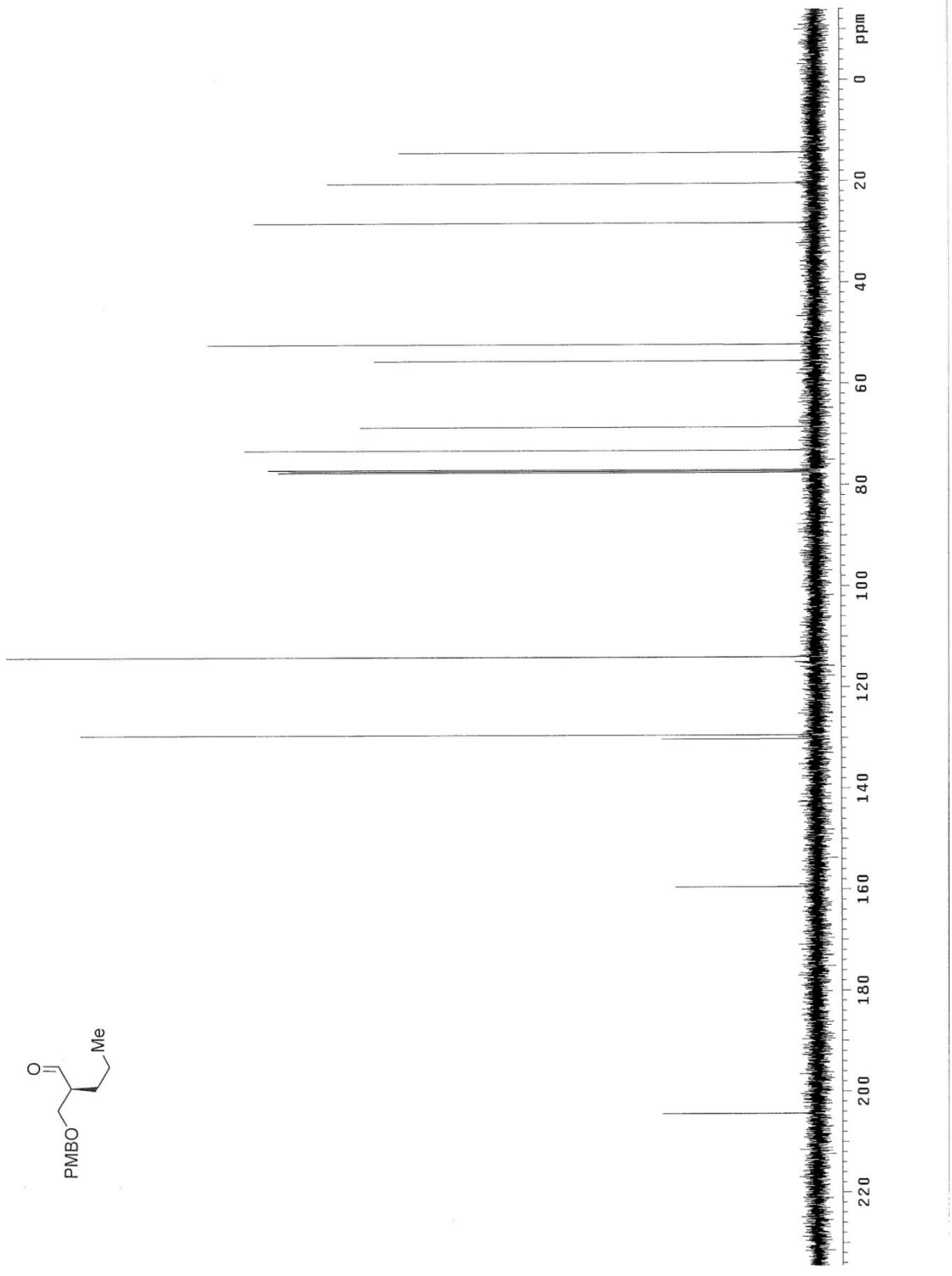
ppm


PMBO
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Me
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0
20
40
60
80
100
120
140
160
180
200
220

Chapter 4

Development of Nickel-Catalyzed Borylative Ketone Diene Coupling Reactions[1]

4.1 Introduction

Metal-catalyzed multi-component coupling reactions can rapidly construct complex molecules from simple substrates, and are regarded as one of the most attractive and valuable strategies in organic syntheses. In particular, multi-component coupling reactions involving a di-π-components can construct complex molecules not only in a stereo- and regioselective fashion, but also provide stereodefined versatile olefins. Pioneered by Mori[2] and Tamaru,[3] catalytic reductive coupling reactions involving organometallic reagents (M-R) or metal hydrides (M-H) have expanded on earlier work by Sato[4] and Montgomery[5] (Scheme 4.1, equation 1). More recently, it was revealed that incorporating a dimetalic reagent (e.g. R_2B-BR_2, R_2B-SiR_3, R_3Si-SnR_3) to this reaction generated an additional valuable allylmetal moiety that can be used to further build molecule complexity (Scheme 4.1, equation 2).[6]

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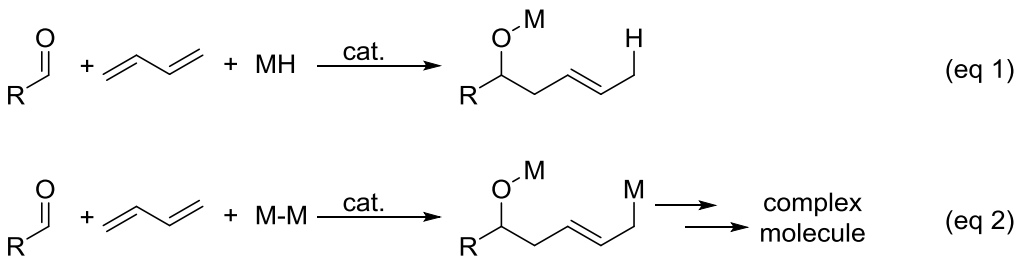
[1] Part of this project has been published: Cho, H. Y.; Yu, Z.; Morken, J. P. *Organic Letters* **2011**, *13*, 5267.
[2] Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc*. **1994**, *116*, 9771.
[3] Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc*. **1998**, *120*, 4033.
[4] Ikeda, S.; Sato, Y. *J. Am. Chem. Soc*. **1994**, *116*, 5975.
[5] Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099.
[6] For a recent review, see: Cho, H. -Y.; Morken, J. P. *Chem. Soc. Rev.* **2014**, *43*, 4368.

Scheme 4.1. Reductive and Bismetallative Multicomponent Coupling Reactions



4.2 Background

Diene-carbonyl coupling reactions have been extensively studied and these transformations were carried out under reductive conditions with either silane reagents and organozinc reductants,[7] or organoboronate reagents.[8] Thus, these transformations won't be covered here. Instead, metal catalyzed multicomponent cross coupling reactions involving carbonyls, di-π-systems and dimetal reagents are discussed below.

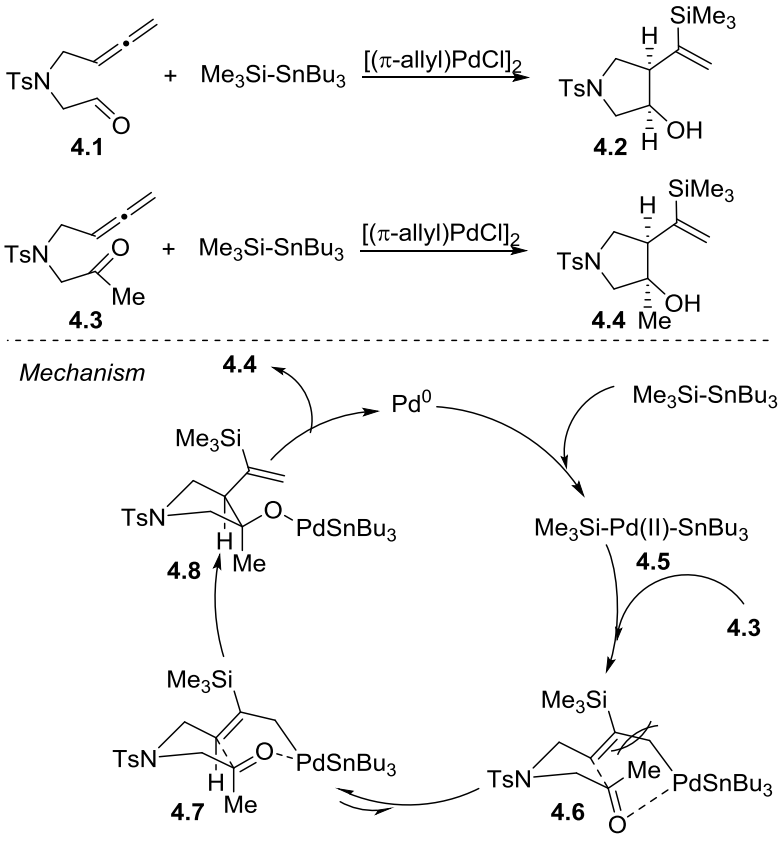
4.2.1. Intramolecular Bismetallative Carbonyl Di-π-Component Reactions

In 2002, Kang and co-workers disclosed a Pd-catalyzed carbonyl-allene cyclization using a Sn-Si reagent (Scheme 4.2).[9] When the allenyl aldehyde **4.1** was treated with $Me_3Si\text{-}SnBu_3$ in the presence of catalytic $[(\pi\text{-allyl})PdCl]_2$ at ambient temperature, it underwent silastannylative coupling efficiently to produce *cis*-cyclopentanol **4.2** with good yield and stereoselection. An even more challenging substrate (**4.3**) containing a sterically hindered and less reactive ketone electrophile also participated in this coupling reaction, furnishing the tertiary-alcohol product **4.4**. The

[7] (a) For a recent review on reductive multicomponent reactions, see: de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev*. **2012**, *41*, 3969. (b) Montgomery, J. *Angew. Chem. Int. Ed*. **2004**, *43*, 3890.
[8] (a) Saito, N.; Yamazaki, T.; Sato, Y. *Chem. Lett*. **2009**, *38*, 594. (b) Saito, N.; Yamazaki, T.; Sato, Y. *Tetrahedron Lett*. **2008**, *49*, 5073.
[9] Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y. Jung, J. *Angew. Chem. Int. Ed*. **2002**, *41*, 343.

mechanism is proposed in Scheme 4.2 and begins with palladium (0) oxidatively inserting in the Sn-Si bond, producing Me_3Si-Pd(II)-$SnBu_3$ (**4.5**) intermediate. Subsequent addition across allene **4.3** gave an allylpalladium intermediate **4.7**, a more stable form than **4.6**, avoiding the interaction between the methyl and TMS groups, resulting in a cisoid intermediate. Finally, allylpalladium **4.7** undergoes intramolecular allylation to furnish alkoxyl-palladium **4.8** that gives *cis*-cyclopentanol **4.4** after reductive elimination and workup.

Scheme 4.2. Kang's Intramolecular Carbonyl-Allene Coupling and Proposed Mechanism



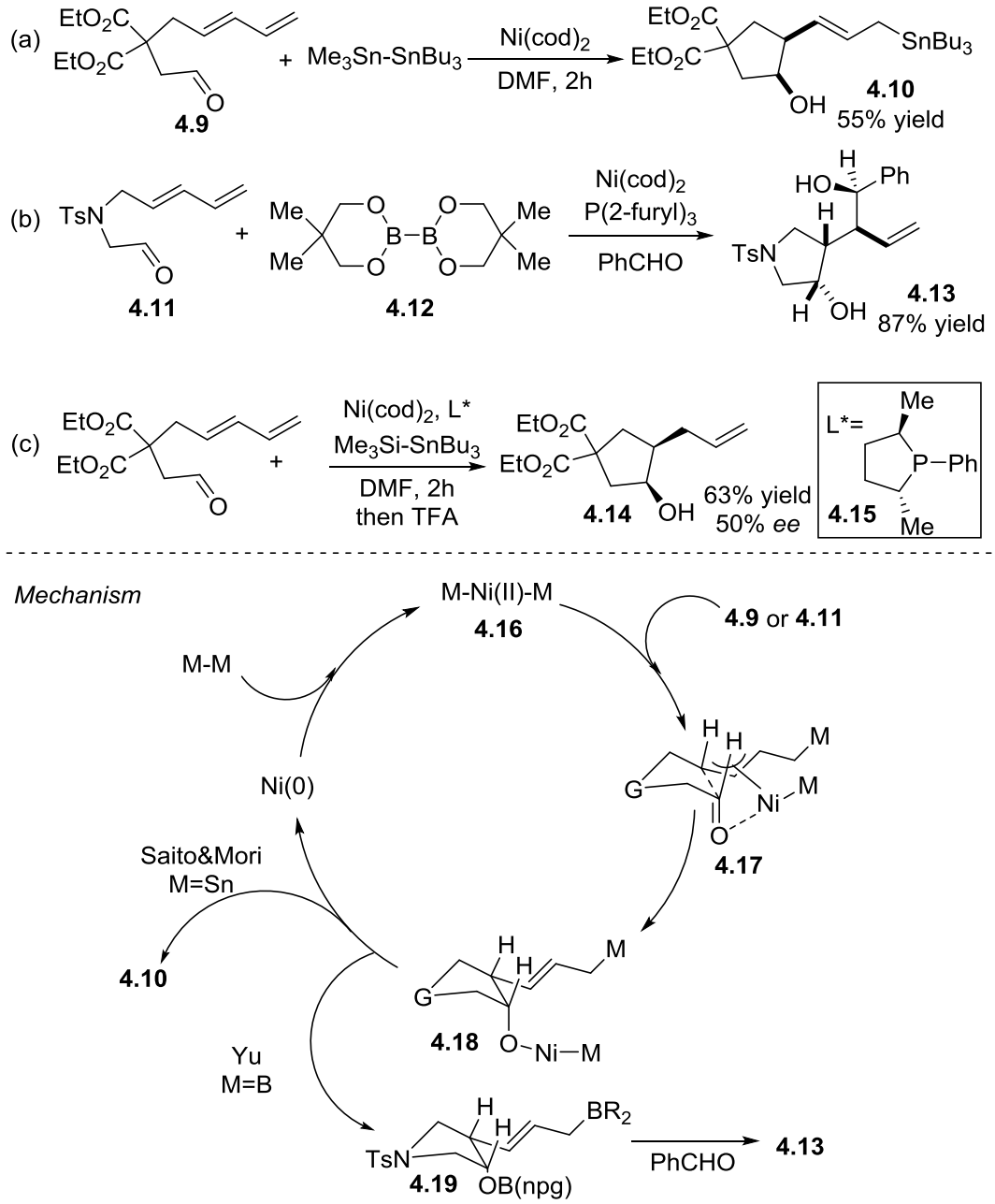
An intramolecular coupling of a diene and an aldehyde was reported by Mori and co-workers (Scheme 4.3a).[10] In the presence of a catalytic amount of nickel (0) and 1.0 equivalent Me_3Sn-$SnBu_3$ reagent, dienal **4.9** cyclized to generate a *cis*-cyclopentanol **4.10**

[10] Sato, Y.; Saito, N.; Mori, M. *Chem. Lett.* **2002**, 18.

with moderate yield. As mentioned above, one of the advantages of using a dimetallic reagent in diene-aldehyde coupling reaction is that a versatile allylmetal moiety is embedded in the product, which can be further functionalized (Scheme 4.1). Yu and co-workers have taken advantage of this by trapping the allylmetal intermediate *in situ* with benzaldehyde, thereby furnishing adduct **4.13** with good yield and diastereoselectivity (Scheme 4.3b).[11] The reaction mechanism is proposed in Scheme 4.3. Beginning with nickel (0) oxidative addition to the dimetal reagent, a diene insertion provides a π-allyl intermediate **4.17**. Subsequent intramolecular allylation with the aldehyde gives cyclized compound **4.18**. In the absence of additional aldehyde (e.g. benzyladehyde), *cis*-cyclopentanol **4.10** was generated after reductive elimination of **4.18**; otherwise, the reaction proceeded further after reductive elimination of **4.18**. The intermediate allylboronic ester **4.19** underwent a second allylation with the additional aldehyde to furnish **4.13**. It is worth pointing out that the corresponding cyclized product **4.14** can be prepared with moderated enantiomeric excess (50% *e.e.*) when the chiral monodentate ligand **4.15** was used (Scheme 4.3c).[12]

[11] Yu, C.-M.; Youn, J.; Yoon, S.-K.; Hong, Y.-T. *Org. Lett*. **2005**, *7*, 4507.
[12] Saito, N.; Mori, M.; Sato, Y. *J. Organomet. Chem*. **2007**, *692*, 460.

Scheme 4.3. Mori and Yu's Intramolecular Carbonyl-Diene Coupling and Proposed Mechanism

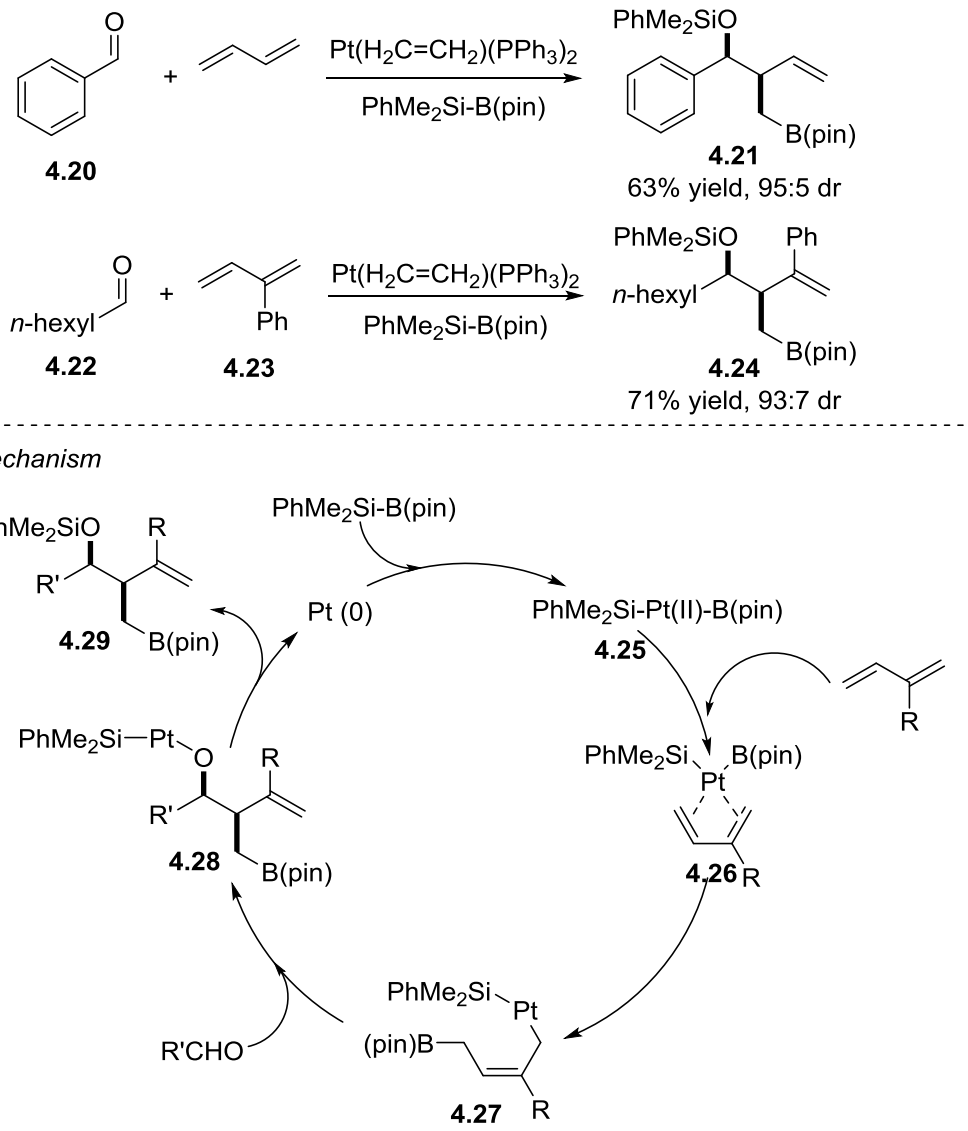


4.2.2. Intermolecular Bismetallative Carbonyl Di-π-Component Reactions

Ito and co-workers have developed a Pt-catalyzed silaborative intermolecular aldehyde-diene coupling reaction.[13] In the presence of catalytic Pt(ethylene)(PPh_3)$_2$, a 1,3-diene (symmetrical butadiene or unsymmetrical diene **4.23**), an aldehyde (aromatic **4.20** or aliphatic **4.22**) and $PhMe_2Si$-B(pin) were successfully assembled together regioselectively, furnishing a highly diastereoselective homoallylic alcohol (**4.21** or **4.24**). The proposed mechanism is shown in Scheme 4.4. Platinum (0) oxidatively adds to the Si-B bond to form $PhMe_2Si$-Pt(II)-B(pin) (**4.25**), which coordinates to the *s-cis* conformer of 1,3-diene (**4.26**). Subsequent diene migratory insertion into the Pt-B bond forms a C-B bond at the terminal carbon of less hindered olefin to provide the *cis*-allylplatinum **4.27**. This platinum complex then reacts with an aldehyde followed by reductive elimination to afford desired product **4.29** and regenerate the platinum (0) catalyst.

[13] Suginome, M.; Nakamura, H.; Matsuda, T.; Ito, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4248.

Scheme 4.4. Ito's Intermolecular Carbonyl-Diene Coupling and Proposed Mechanism

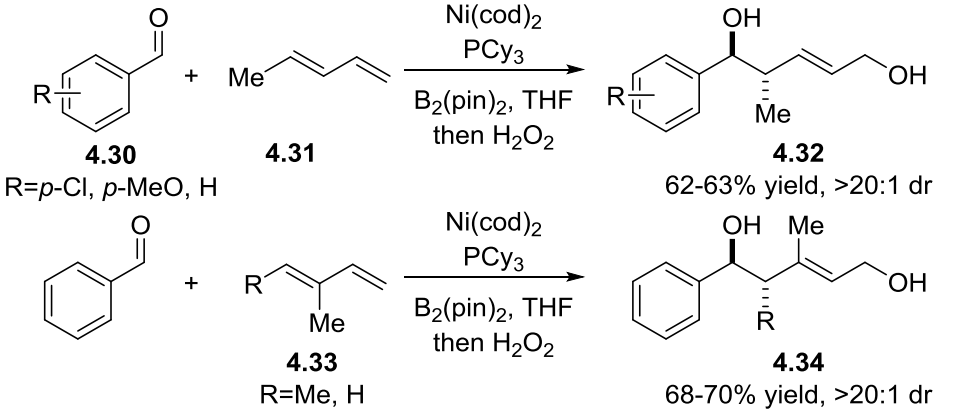


Morken and co-workers developed a borylative diene-aldehyde three-component coupling reaction in 2008 (Scheme 4.5).[14] Various aromatic aldehydes (**4.30**) participated in this reaction as well as different substituted 1,3-dienes (**4.31** and **4.33**), which gave highly diastereoselective 1,5-diols (**4.32** and **4.34**) after oxidation (Scheme 4.5).[14a] The homoallylic alcohol products with adjacent *anti*-propionate moieties are valuable

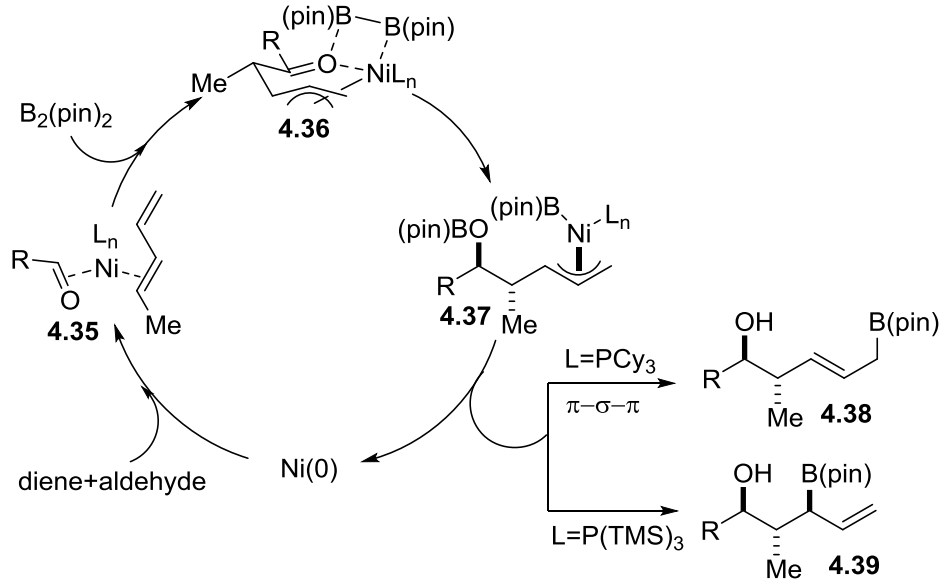
[14] (a) Cho, H. Y. Morken, J. P. *J. Am. Chem. Soc*. **2008**, *130*, 16140. (b) Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 7576.

building blocks for organic syntheses (Chapter 1). The mechanism is proposed as shown in Scheme 4.5, which is different compared to the above examples. Initial oxidative cyclization between the diene and aldehyde delivers nickelacycle **4.36** from a nickel complex **4.35**, which then undergoes σ-bond metathesis with a diboron reagent to provide a nickel π-allyl intermediate **4.37**. Subsequent π-σ-π rearrangement and reductive elimination gives allylboronic ester **4.38** when PCy_3 is used as phosphine ligand.

Scheme 4.5. Morken Borylative Diene Aldehyde Coupling and Proposed Mechanism

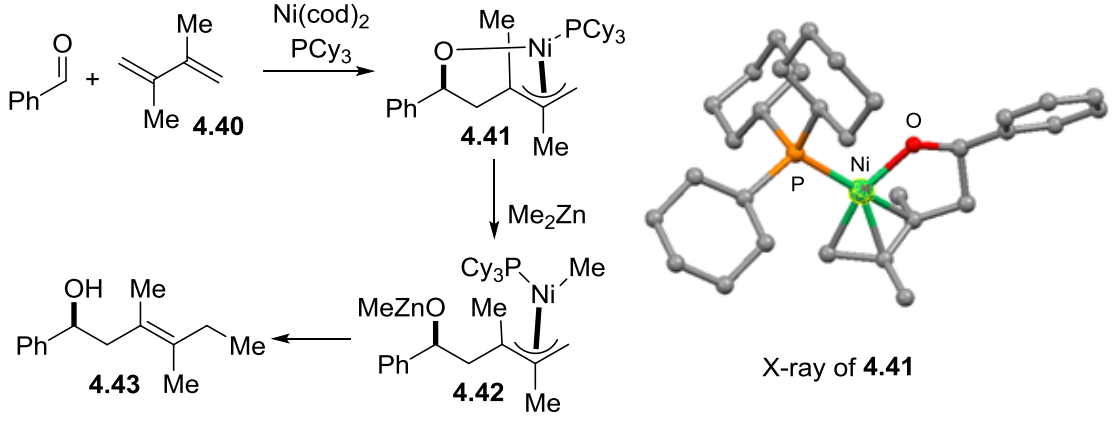


proposed mechanism



This proposed mechanism was supported by X-ray crystallography of a structurally similar complex **4.41**, which was prepared by treating benzaldehyde and diene **4.40** with stoichiometric $Ni(cod)_2$ (Scheme 4.6).[15] After addition of an alkylmetal reagent, Me_2Zn, the complex **4.41** was reduced to Ni-π-allyl intermediate **4.42** followed by reductive elimination to afford homoallyl alcohol **4.43**. This study has secured the proposed mechanism for borylative diene-aldehyde coupling reaction shown in Scheme 4.5.

Scheme 4.6. Support for Morken Proposed Mechanism

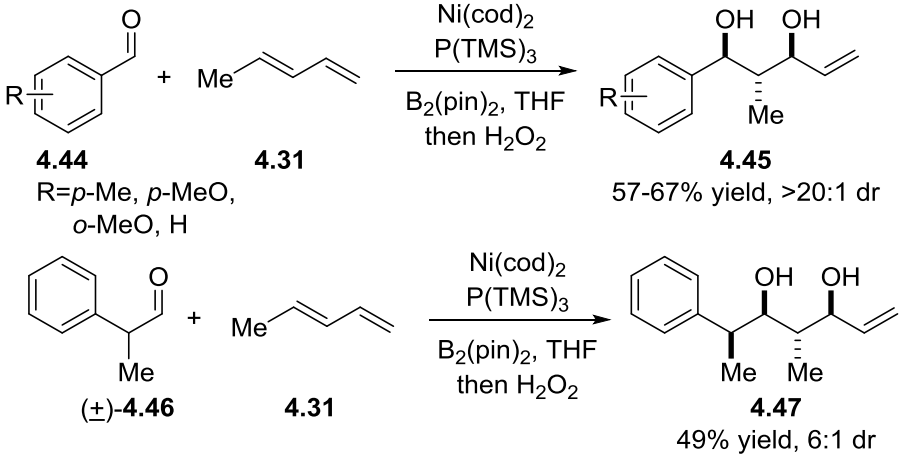


Interestingly, changing the phosphine ligand from PCy_3 to $P(TMS)_3$ resulted in a different regioisomeric product (**4.45**) from the diboron promoted cross coupling reaction (Scheme 4.7).[14b] A number of aromatic aldehydes participated in this reaction and constructed highly diastereoselective 1,3-diols (**4.45**). The coupling reactions with aliphatic aldehydes were also effective but with slightly lower yield under the same reaction conditions (results not shown). Moreover, α-chiral aldehyde **4.46** participated in this reaction giving **4.47** with Felkin selectivity[16] and rapidly delivering a *syn/anti/anti*-stereotetrad moiety that maps onto various polyketide natural products. The power of this

[15] Ogoshi, S.; Tonomori, K.; Oka, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2006**, *128*, 7077.
[16] Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett*. **1968**, *9*, 2199.

transformation has already been demonstrated in the total synthesis of (+)-discodermolide (Chapter 2). The formation of the different regioisomers is due to the unique properties of $P(TMS)_3$: it has a large cone angle and electron accepting ability,[17] which facilitate reductive elimination to furnish1,3-diol **4.39** before allyl isomerization of **4.37** that will lead to 1,5-diol **4.38** (Scheme 4.5).

Scheme 4.7. Ligand Effect on Regioselectivity

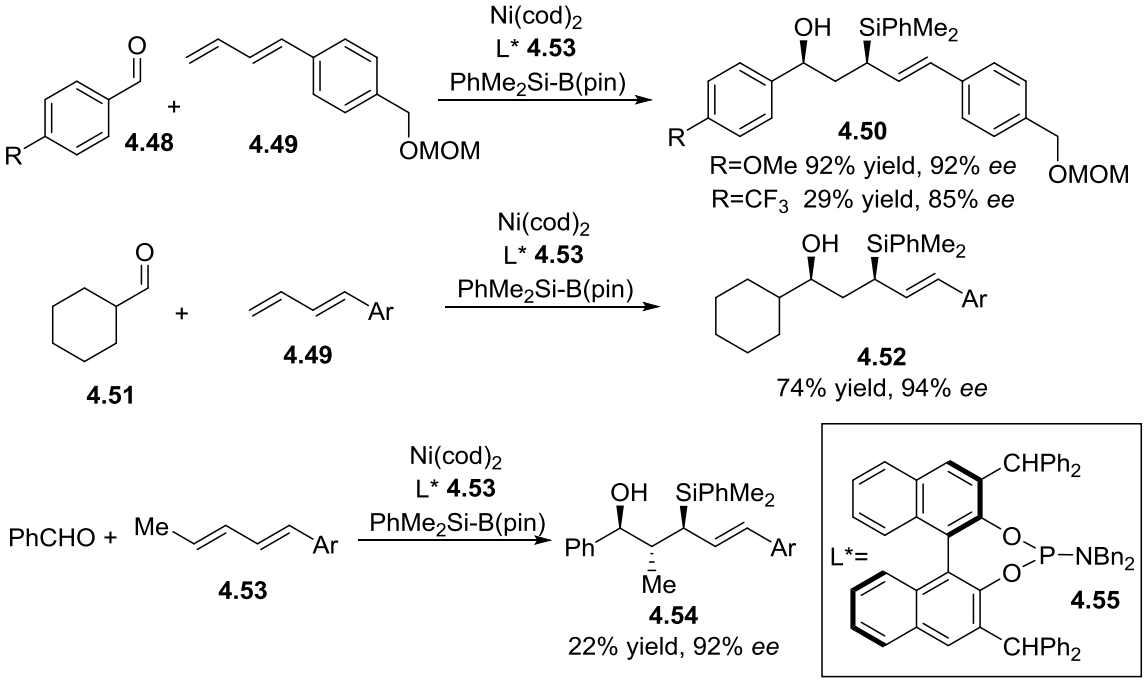


A Ni-catalyzed enantioselective silaborylative diene-aldehyde coupling reaction was disclosed by Saito and Sato (Scheme 4.8).[18] A silylboron reagent, $PhMe_2Si$-B(pin), was employed in this process along with 1,3-dienes (**4.49** and **4.53**) and aldehydes in the presence of nickel catalyst and chiral phosphoramidite ligand **4.55** (Scheme 4.8). High levels of enantioselectivity were observed for electron rich aromatic aldehyde **4.48-OMe** and aliphatic aldehyde **4.51**; however, electron deficient aldehyde **4.48-CF_3** gave poor yield while maintaining good enantiomeric excess. It is worth noting that the coupling product has an embedded α-chiral allylsilane functionality, making it a useful reagent for

[17] (a) Bartik, T.; Himmler, T.; Schulte, H.-G.; Seevogel, K. *J. Organomet. Chem*. **1984**, *272*, 29. (b) McCampbell, T. A.; Kinkel, B. A.; Miller, S. M. Helm, M. L. *J. Chem. Crystallogr*. **2006**, *36*, 271.
[18] Saito, N.; Kobayashi, A.; Sato, Y. *Angew. Chem. Int. Ed*. **2012**, *51*, 1228.

polyketide synthesis (Chapter 1). Internal diene **4.53** also participated in this reaction to furnish the *anti/anti*-stereotriad **4.54** with high diastereo- and enantioselectivity, albeit in low yield. This coupling reaction represents the first example of intermolecular asymmetric coupling of an aldehyde and di-π-reagent with a bimetallic reagent.

Scheme 4.8. Saito and Sato Asymmetric Diene-Aldehyde Coupling

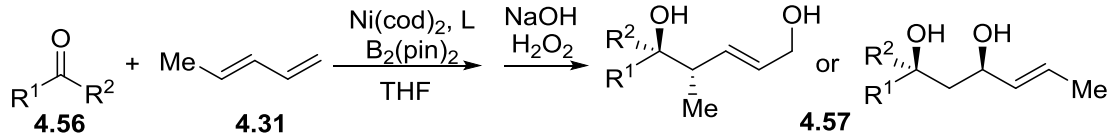


Most of the aforementioned examples employed aldehydes as electrophiles; ketones, on the other hand, are underdeveloped and rarely used in multicomponent coupling reaction, especially in an intermolecular fashion.[19] Since borylative diene-aldehyde coupling reactions worked exceptionally well (Scheme 4.5 and 4.7), it would be

[19] For diene-carbonyl couplings that employ ketones, see: (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc*. **1994**, *116*, 9771. (b) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett*. **1996**, *37*, 887. (c) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed*. **1999**, *38*, 397. (d) Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed*. **1999**, *38*, 3386. (e) Sato, Y.; Takimoto, M.; Mori, M. *J. Am. Chem. Soc*. **2000**, *122*, 1624. (f) Ezoe, A.; Kimura, M.; Inoue, T.; Mori, M.; Tamaru, Y. *Angew. Chem., Int. Ed*. **2002**, *41*, 2784. (g) Kimura, M.; Kojima, K.; Tamaru, Y. *Synthesis* **2004**, 3089. (h) Kimura, M.; Ezoe, A.; Mori, M.; Tamaru, Y. *J. Am. Chem. Soc*. **2005**, *127*, 201. (i) Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc*. **2006**, *128*, 8559.

interesting to apply such strategy to ketone (**4.56**) electrophiles and to determine whether the high stereoselection would be maintained (Scheme 4.9). Moreover, this transformation would provide a synthetically useful product containing the biologically important tertiary alcohol functionality, which is hard to prepare in a diastereoselective fashion.[20]

Scheme 4.9. Proposed Borylative Diene Ketone Coupling



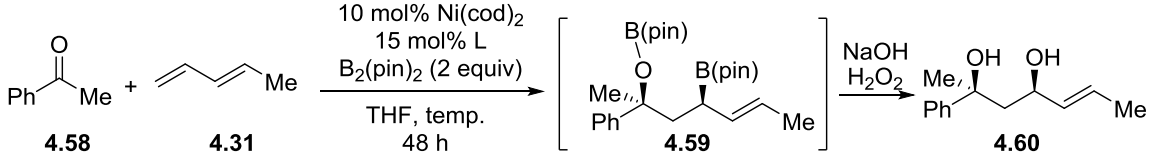
4.3 Development of Ni-Catalyzed Borylative Diene-Ketone Coupling Reactions

Acetophenone **4.58** and *trans*-pentadiene **4.31** were chosen as model substrates to initiate the proposed ketone-diene coupling reaction. We first evaluated a number of monodentate phosphine ligands which were known to play an important role in metal catalyzed reactions (Table 4.1, entry 1-6). Under similar reaction conditions shown in Scheme 4.5 and 4.7 (10 mol % $Ni(cod)_2$, 15 mol % ligand, 2.0 equiv $B_2(pin)_2$ in THF), tri-*tert*-butylphosphine was the only ligand that afforded the desired tertiary alcohol product **4.60** with good yield and excellent diastereoselectivity after oxidative work-up (Table 4.1, entry 6). In addition to achiral phosphines, several chiral monodentate ligands were tested and proved to be non-effective (data not shown). The multicomponent coupling reaction was also temperature dependent (Table 4.1, entry 6-8). Lower reaction temperature (0 ^{o}C) caused diminished conversion (Table 4.1, entry 7), while elevated

[20] (a) Garcia, C.; Martin, V. S. *Curr. Org. Chem.* **2006**, *10*, 1849. (b) Riant, O.; Hannedouche, J *Org. Biomol. Chem.* **2007**, *5*, 873. (c) For selected review, see: Shibasaki, M.; Kanai, M. *Chem.l Rev.* **2008**, *108*, 2853.

temperature proved to be detrimental to diastereoselectivity (Table 4.1, entry 8). It was also crucial to use excess diboron reagent to obtain good yield in a reasonable reaction time period. Thus, the most effective reaction condition was identified as using P(*t*-Bu)$_3$ ligand at room temperature for nickel-catalyzed borylative diene-ketone three-component coupling reaction.

Table 4.1. Reaction Condition Screening



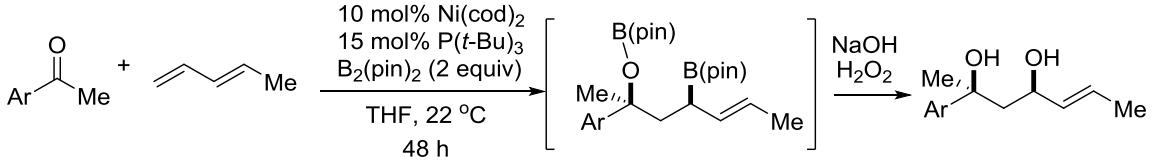
entry	ligand	temperature	yield (%)[a]	dr[b]
1	PCy_3	rt	0	n/a
2	$P(OEt)_3$	rt	0	n/a
3	PPh_3	rt	0	n/a
4	$P(TMS)_3$	rt	0	n/a
5	PMe_3	rt	0	n/a
6	P(*t*-Bu)$_3$	rt	76	>20:1
7	P(*t*-Bu)$_3$	0 ^oC	<20	n/a
8	P(*t*-Bu)$_3$	60 ^oC	47	5:1

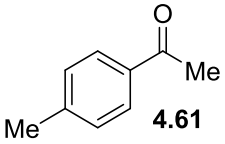
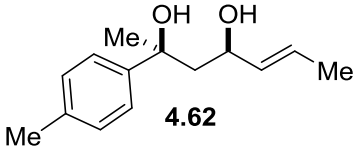
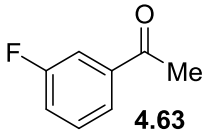
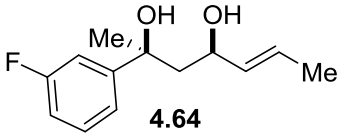
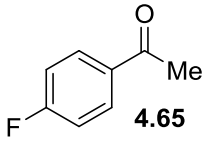
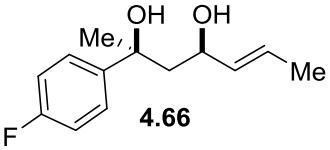
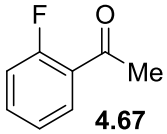
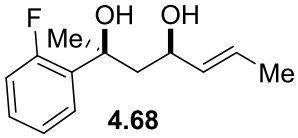
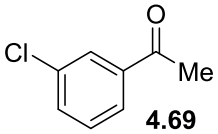
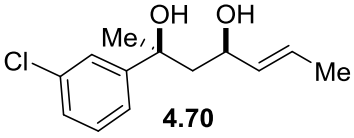
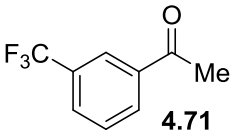
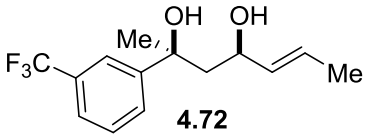
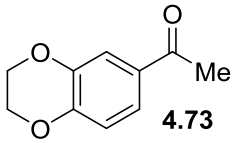
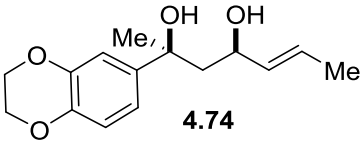
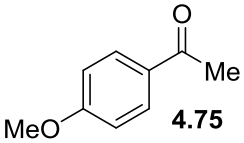
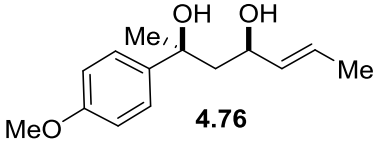
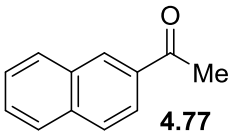
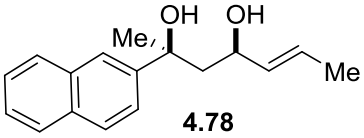
[a] yields refer to isolated yield of purified material. [b] stereoselectivity determined by ^1H NMR analysis.

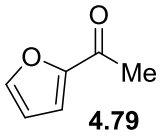
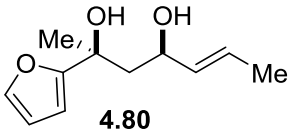
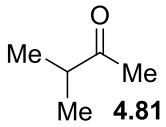
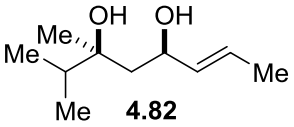
With optimized reaction conditions in hand, a number of substrates were examined for this ketone-diene coupling reaction. Various acetophenone derivatives were tested, and, pleasingly, they participated in the multicomponent coupling reaction to afford tertiary alcohol containing products with good yield and excellent diastereo-selectivity (Table 4.2). *Para*-methyl substitution (**4.61**) was tolerated (Table 4.2, entry 1) as well as fluorine substitution on any position of the phenyl ring (*ortho*-**4.67**, *meta*-**4.63**, *para*-**4.65**) (Table 4.2, entry 2-4). Aryl chloride moiety (**4.69**) also survived in this nickel

catalysis to deliver the corresponding 1,3-diol **4.70** (Table 4.2, entry 5). Furthermore, aromatic rings with either highly electron-withdrawing (**4.71**) or electron-donating groups (**4.73** and **4.75**) were also competent reaction partners for this transformation (Table 4.2, entry 6-8). Besides substituted benzene rings, 2-naphthyl (**4.77**) and 2-furyl (**4.79**) substituted methyl ketones were successfully coupled with *trans*-pentadiene and $B_2(pin)_2$ to afford the corresponding tertiary alcohols (Table 4.2, entry 9 and 10). In all cases surveyed, >20:1 *syn:anti* diastereoselectivity was observed in the coupling reaction products.

Table 4.2. Borylative Coupling Reactions with Aryl Methyl ketones



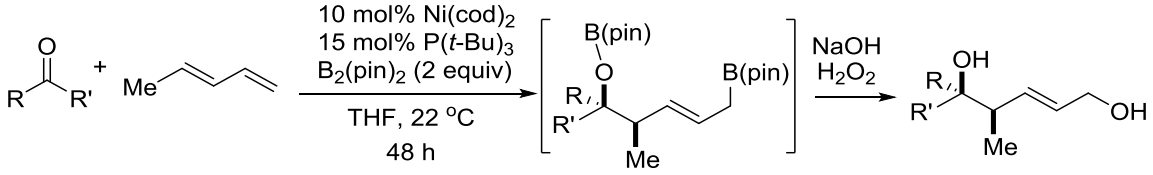
entry	substrate	product	yield (%)[a]	dr[b]
1	 **4.61**	 **4.62**	79	>20:1
2	 **4.63**	 **4.64**	73	>20:1
3	 **4.65**	 **4.66**	71	>20:1
4	 **4.67**	 **4.68**	70	>20:1
5	 **4.69**	 **4.70**	63	>20:1
6	 **4.71**	 **4.72**	63	>20:1
7	 **4.73**	 **4.74**	69	>20:1
8	 **4.75**	 **4.76**	52	>20:1
9	 **4.77**	 **4.78**	72	>20:1

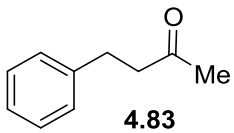
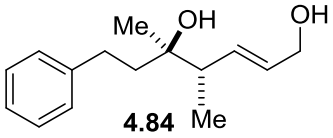
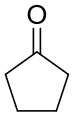
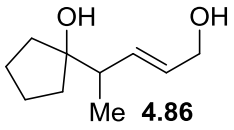
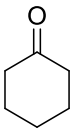
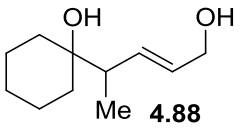
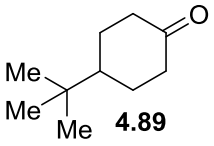
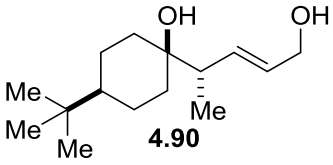
10	 **4.79**	 **4.80**	51	>20:1
11	 **4.81**	 **4.82**	24	>20:1

[a] yields refer to isolated yield of purified material; value is an average of two or more experiments. [b] stereoselectivity was determined by ^{1}H NMR analysis.

Whereas functionalized aryl methyl ketones formed highly diastereoselective 1,3-diols with good yield and stereoselection, dialkylketones delivered regioisomeric 1,5-diols (Table 4.3). For example, 4-phenyl-2-butanone (**4.83**) (Table 4.3, entry 1) underwent cross coupling with *trans*-pentadiene and $B_2(pin)_2$ to furnish the 1,5-diol **4.84** in a connection similar to that observed for reactions of benzaldehyde (Scheme 4.5). This outcome is in contrast to the regioselectivity of aryl methyl ketones (Table 4.2). It was suspected that the reversal in C-C bond connection forming the 1,5-diol occurred because of lowered steric encumberance of the carbonyl. To test this hypothesis, the more sterically hindered ketone, 3-methyl-2-butanone **4.81**, was subject to the reaction conditions; as expected, 1,3-diol **4.82** was formed which is the same regioisomeric product produced from hindered aryl methyl ketones (Table 4.2, entry 10). Constrained cyclic ketones also gave 1,5-diol products with good yield (Table 4.3, entry 2 and 3). It is worth pointing out that the product of 4-substituted cyclohexanone **4.89** appears to arise by preferred equatorial attachment of the diene to the carbonyl carbon of the substrate leading to high diastereoselectivity.

Table 4.3. Borylative Coupling Reactions with Diakylketones

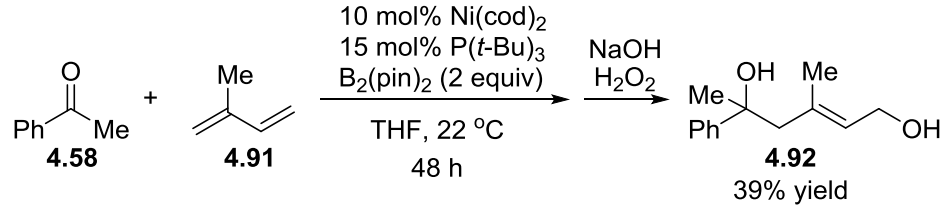


entry	substrate	product	yield (%)[a]	dr[b]
1	 **4.83**	 **4.84**	69	7:1
2	 **4.85**	 **4.86**	56	-
3	 **4.87**	 **4.88**	52	-
4	 **4.89**	 **4.90**	53	>20:1

[a] yields refer to isolated yield of purified material; value is an average of two or more experiments. [b] stereoselectivity determined by ^{1}H NMR analysis.

In the same context, when isoprene **4.91** was employed in the multicomponent coupling reaction instead of *trans*-pentadiene, 1,5-diol **4.92** was produced, albeit in lower yield (Scheme 4.10).

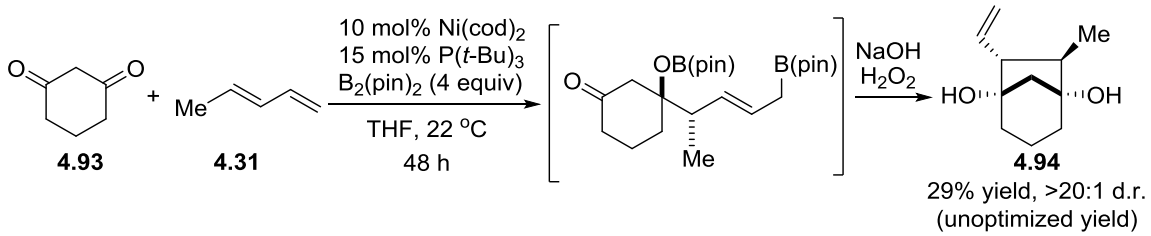
Scheme 4.10. Borylative Coupling Reaction with Acetophenone and Isoprene



As mentioned above, the borylative diene-ketone coupling reactions constructed not only the challenging tertiary alcohol moiety but also a synthetically useful allylboronic ester. So far, the only utility demonstrated for the versatile allylboron substituent has been the oxidation to allylic alcohols (Table 4.2 and 4.3); however, allylboronic esters can participate in various transformations, such as allylation with a carbonyl (Chapter 1). Thus, it was considered that in the presence of a second carbonyl group, a cascade intramolecular allylation would take place.[21] To initiate the borylative bisketone-diene coupling reactions, 1,3-cyclohexanedione **4.93** was treated with *trans*-pentadiene **4.31** and $B_2(pin)_2$ in the presence of catalytic $Ni(cod)_2$ and P(*t*-Bu)$_3$ (Scheme 4.11). We were pleased to see that both the three-component coupling reaction and a cascade intramolecular allylation worked smoothly to provide a bicyclic molecule (**4.94**) with moderate yield and excellent diastereoselectivity. This tandem reaction directly constructed a structurally, functionally, and stereochemically enriched product whose synthesis would otherwise require multiple steps.

[21] For similar strategy, see: Ferris, G. E.; Hong, K. Roundtree, I. A. Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 2501.

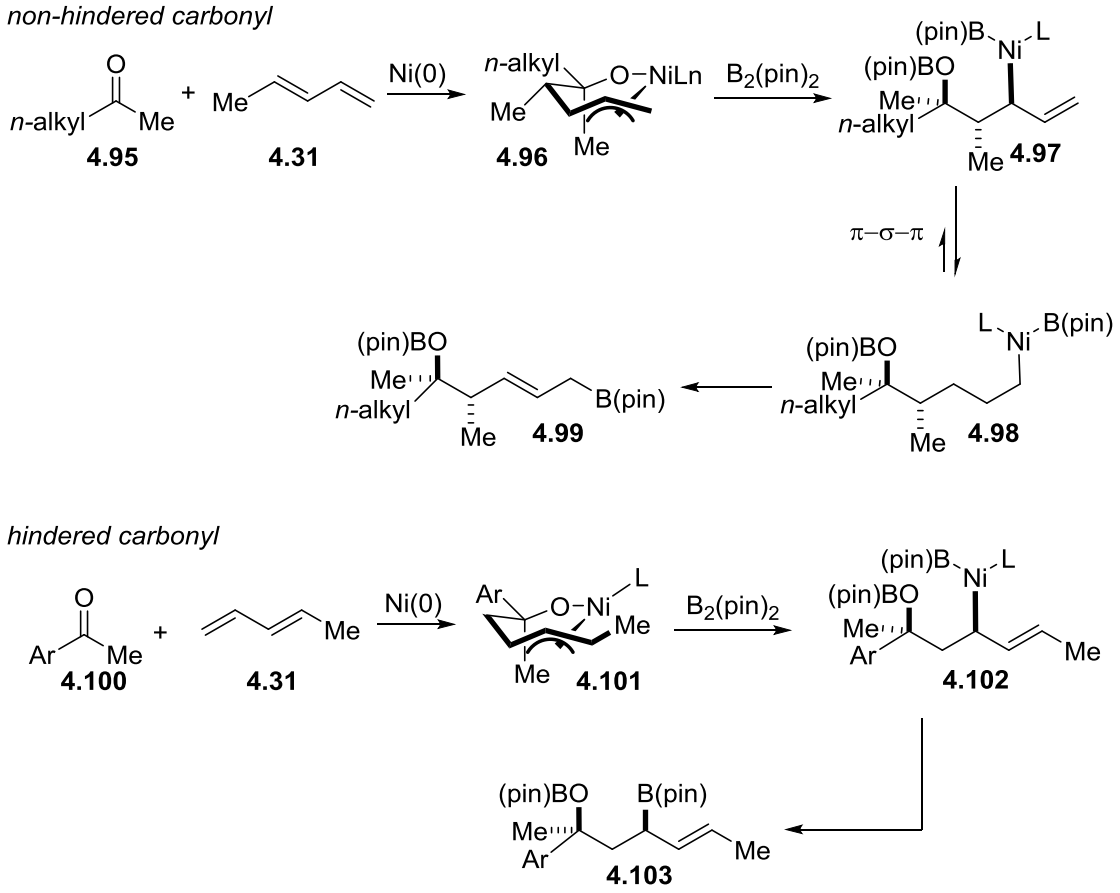
Scheme 4.11. Tandem Bisketone-Diene Coupling/Allylation Reaction



Due to the similarities of this reaction and the borylative diene-aldehyde coupling reactions (Scheme 4.5 and Scheme 4.7), they should share similar mechanism which can be used to understand the different regiochemical outcome of the coupling processes with hindered and non-hindered carbonyl substrates (Scheme 4.12). The reaction of less hindered carbonyl **4.95** with *trans*-pentadiene **4.31** occurs to give a nickelacycle **4.96**. Subsequent σ-bond metathesis with $B_2(pin)_2$ delivers an intermediate **4.97**, which undergoes fast π-σ-π isomerization prior to reductive elimination, providing Ni-complex **4.98**. This complex then gives 1,5-bisboronate **4.99** after reductive elimination.

For more hindered carbonyls **4.96**, it is tenable that steric effects retard C-C bond formation with the substituted terminus of the diene **4.31** and, instead, the less hindered end of the diene **4.31** adds to carbonyl. The formation of this new C-C bond leads to a nickelacycle **4.101**, and subsequent σ-bond metathesis gave a nickel-complex intermediate **4.102**, a compound that undergoes reductive elimination furnishing 1,3-bisboronic ester **4.103**. It is conceivable that, with a substituted allyl metal as in **4.102**, the π-σ-π isomerization is retarded relative to reductive elimination and the geometry of the initial bond metathesis product **4.102** dictates the regiochemical outcome of the reaction.

Scheme 4.12. Proposed Reaction Mechanism for Diene-Ketone Coupling Reactions



4.4 Conclusion

We have extended the borylative carbonyl-diene coupling reaction to less reactive ketone substrates and that it occurs in a regio- and stereoselective fashion. Moreover, the regioselection for different ketone substrates has been explained by the known mechanism, which can serve as a guide to predict the reaction outcome. This multicomponent coupling reaction delivers corresponding product with synthetically valuable tertiary alcohol as well as allyl alcohol/allyl boronic ester. In the presence of a second carbonyl, the embedded allyl boronic ester in the ketone-diene coupling product could participate in a cascade reaction to construct a highly diastereoselective bicyclic compound.

The future work would focus on synthesizing an efficient chiral phosphine ligand for asymmetric borylative carbonyl-diene coupling reaction, providing a new route for polyketide natural product syntheses (Chapter 1).

4.5. Experimental Procedure

General Information

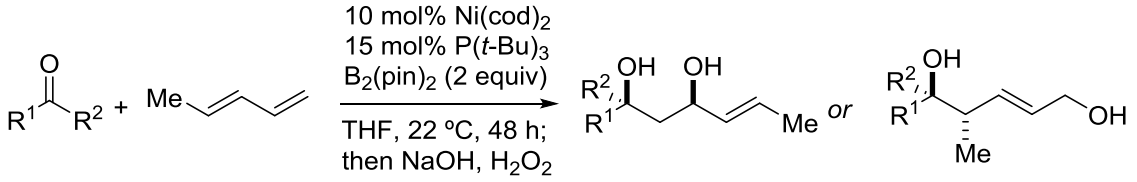
^{1}H NMR spectra were recorded on either a Varian Gemini-400 (400 MHz), or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm, C_6D_6: 7.16 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, br = broad, and m = multiplet), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on either a Varian Gemini-400 (100 MHz), or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.23 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer, ν_{max} cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). High resolution mass spectrometry was performed at the Mass Spectrometry Facility, Boston College, MA.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 40-63 μm) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid (PMA) in ethanol, potassium permanganate ($KMnO_4$) in water, or cerium (IV) sulfate and ammonium molybdate in sulfuric acid.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran (THF), dichloromethane, and diethyl

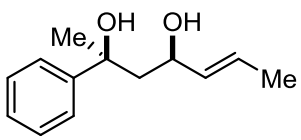
ether were purified using a Pure Solv MD-4 solvent purification system from Innovative Technology Inc. Bis(pinacolato)diboron [$B_2(pin)_2$] was obtained from AllyChem Co., Ltd. and recrystallized from pentane prior to use. Ketones were purchased from Aldrich and distilled/recrystallized prior to use. Bis(1,5-cyclooctadiene)nickel(0) [$Ni(cod)_2$] and phosphine ligands were purchased from Strem Chemicals, Inc. and used without further purification. 1,3-*trans*-pentadiene was purchased from ChemSampCo and distilled prior to use. All other reagents were purchased from either Fisher or Aldrich and used without further purification.

I. General Procedure for Borylative Ketone–Diene Coupling



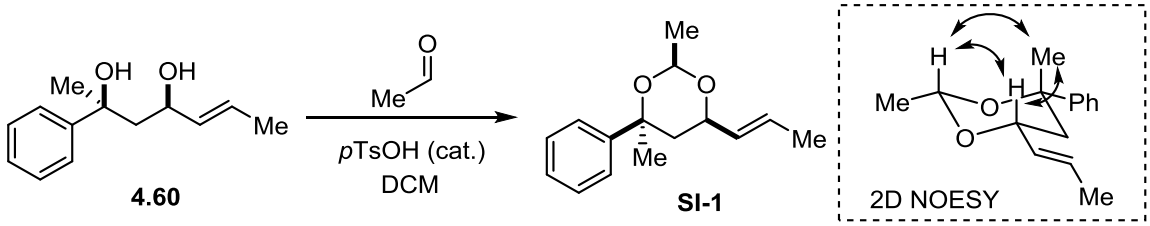
An oven-dried 20 mL scintillation vial, equipped with a magnetic stir-bar, was charged with $Ni(cod)_2$ (0.05 mmol, 0.10 equiv), P(*t*-Bu)$_3$ (0.075 mmol, 0.15 equiv), and THF (2.5 mL, 0.2 M) in a dry box under an argon atmosphere. After stirring for 5 min, the ketone (0.5 mmol. 1.0 equiv), *trans*-1,3-pentadiene (1.0 mmol, 2.0 equiv), and $B_2(pin)_2$ (1.0 mmol, 2.0 equiv) were added sequentially. The vial was sealed with a polypropylene cap and removed from the dry box. The reaction mixture was then allowed to stir at ambient temperature for 48 h. After this time, the mixture was cooled to 0 ^oC (ice-water bath), and 2 mL of 3 M NaOH and 1.5 mL of 30% H_2O_2 were added dropwise with caution. The mixture was then allowed to stir at ambient temperature for 10 h. The resulting solution was cooled to 0 ^oC and quenched by the addition of 2 mL of saturated aqueous $Na_2S_2O_3$. The two-phase mixture was extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was evaporated *in vacuo*. The crude material was purified by silica gel chromatography (hexanes/EtOAc) to afford the title compounds.

II. Full Characterization Data of Products

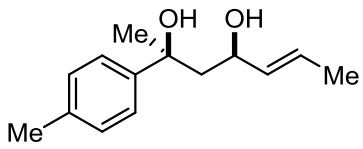


(2*S,4*R**,*E*)-2-Phenylhept-5-ene-2,4-diol (Table 4.1, entry 6)**. The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of $P(t\text{-}Bu)_3$, 60.1 mg (0.5 mmol) of acetophenone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.60** as a colorless oil (78.2 mg, 76% yield). R_f = 0.32 (1:1 hexanes:Et_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 7.46 (2H, d, *J* = 7.5 Hz), 7.34 (2H, t, *J* = 7.0 Hz), 7.23 (1H, t, *J* = 7.0 Hz), 5.68 (1H, dq, *J* = 15.5 Hz, 6.5 Hz), 5.47 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 4.52 (1H, br t, *J* = 7.5 Hz), 3.66 (1H, br s), 2.89 (1H, br s), 1.97 (1H, dd, *J* = 15.0 Hz, 10.0 Hz), 1.85 (1H, dd, *J* = 15.0 Hz, 3.0 Hz), 1.67 (3H, s), 1.66 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.2, 133.9, 128.4, 127.1, 126.8, 124.5, 74.8, 71.0, 49.5, 28.3, 17.7; IR (neat): 3328 (br), 2973 (w), 2915 (w), 1446 (m), 1375 (m), 1211 (m), 1099 (m), 1065 (s), 964 (s), 842 (m), 761 (s), 698 (s), 565 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{15}$ [M–$2H_2O$+H]$^+$: 171.1174, found: 171.1182.

Proof of Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analysis of the spectral data, after conversion of the title compound **4.60** into **SI-1** as shown below.



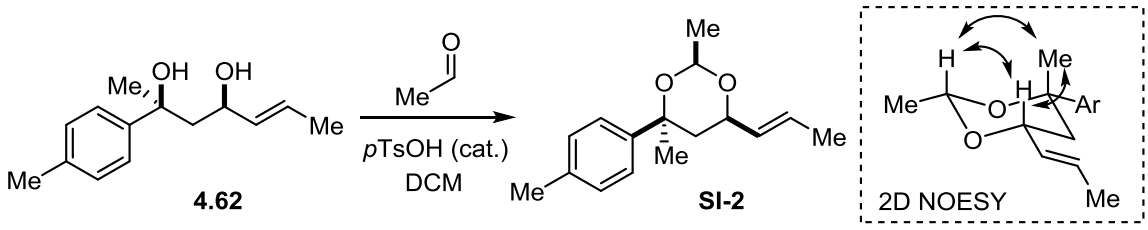
(2*S,4*S**,6*R**)-2,4-Dimethyl-4-phenyl-6-((*E*)-prop-1-en-1-yl)-1,3-dioxane (SI-1)**. A flame-dried 10 mL round-bottom flask, equipped with a magnetic stir-bar, was charged with diol **4.60** (59.8 mg, 0.29 mmol, 1 equiv), acetaldehyde (25.5 mg, 0.58 mmol, 2 equiv), *p*-toluenesulfonic acid (2.9 mg, 0.015 mmol, 0.05 equiv), and dichloromethane (1.5 mL, 0.2 M). After stirring at ambient temperature for 6 h, a saturated aqueous $NaHCO_3$ solution was added. The reaction mixture was extracted with diethyl ether (3 × 10 mL) and the organic layer was washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4. The drying agent was removed by filtration and the solvent was evaporated *in vacuo*. The crude product was purified by silica gel chromatography to afford **SI-1** as a colorless oil. R_f = 0.23 (9:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (2H, d, *J* = 8.5 Hz), 7.34 (2H, t, *J* = 8.5 Hz), 7.24 (1H, t, *J* = 8.5 Hz), 5.79 (1H, dq, *J* = 15.5 Hz, 6.5 Hz), 5.49 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 5.25 (1H, q, *J* = 5.0 Hz), 4.37-4.33 (1H, m), 1.83 (1H, dd, *J* = 13.5 Hz, 3.0 Hz), 1.77 (1H, dd, *J* = 14.0 Hz, *J* = 11.5 Hz), 1.71 (3H, d, *J* = 6.0 Hz), 1.63 (3H, s), 1.44 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.9, 131.2, 128.5, 128.3, 126.8, 124.1, 92.3, 74.6, 73.6, 42.0, 23.2, 21.8, 17.9; IR (neat): 2980 (w), 2934 (w), 2852 (w), 1495 (w), 1447 (m), 1405 (w), 1378 (w), 1173 (m), 1121 (s), 1042 (w), 969 (s), 937 (w), 763 (m), 676 (s), 544 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{15}H_{24}NO_2$ $[M+NH_4]^+$: 250.1807, found: 250.1806.



(2*S,4*R**,*E*)-2-(*p*-Tolyl)hept-5-ene-2,4-diol (Table 4.2, entry 1)**. The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 67.1 mg (0.5 mmol) of 4′-methylacetophenone, 68.1 mg (1.0 mmol) of *trans*-1,3-

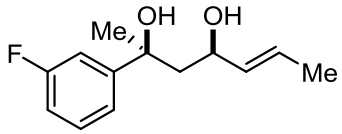
pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.62** as a colorless oil (86.9 mg, 79% yield). R_f = 0.26 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (2H, d, *J* = 8.5 Hz), 7.15 (2H, d, *J* = 8.5 Hz), 5.69 (1H, dq, *J* = 15.5 Hz, 6.5 Hz), 5.48 (1H, dd, *J* = 15.0 Hz, 7.0 Hz), 4.52 (1H, br t, *J* = 7.5 Hz), 3.32 (1H, br s), 2.71 (1H, br s), 2.33 (3H, s), 1.96 (1H, dd, *J* = 15.0 Hz, 10.5 Hz), 1.85 (1H, dd, *J* = 15.0 Hz, 3.0 Hz), 1.67 (3H, d, *J* = 6.0 Hz), 1.66 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.3, 136.4, 134.0, 129.1, 127.0, 124.4, 74.8, 71.0, 49.6, 28.4, 21.1, 17.7; IR (neat): 3331 (br), 2973 (m), 2917 (m), 2883 (w), 1514 (w), 1450 (m), 1420 (m), 1375 (m), 1218 (m), 1207 (m), 1135 (m), 1094 (s), 1074 (s), 1043 (m), 1020 (w), 965 (s), 846 (s), 817 (s), 723 (w), 565 (s), 504 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{14}H_{17}$ $[M–2H_2O+H]^+$: 185.1330, found: 185.1336.

Proof of Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analysis of the spectral data, after conversion of the title compound **4.62** into **SI-2** as shown below.



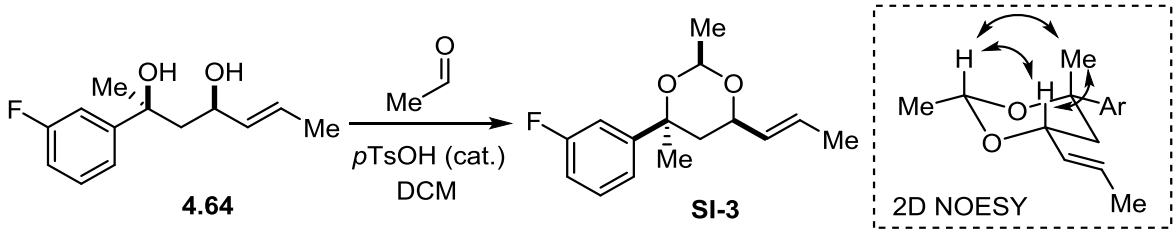
(2*S,4*S**,6*R**)-2,4-Dimethyl-6-((*E*)-prop-1-en-1-yl)-4-(*p*-tolyl)-1,3-dioxane (SI-2)**. The acetonide (**SI-2**) was prepared in the same method as described for acetonide **SI-1**. R_f = 0.22 (9:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (2H, d, *J* = 8.5 Hz), 7.15 (2H, d, *J* = 8.5 Hz), 5.78 (1H, dq, *J* = 15.0 Hz, 6.0 Hz), 5.48 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 5.23 (1H, q, *J* = 5.0 Hz), 4.36-4.32 (1H, m), 2.33 (3H, s), 1.80 (1H, dd, *J* = 13.5 Hz,

3.0 Hz), 1.75 (1H, dd, overlapped), 1.70 (3H, d, J = 6.5 Hz), 1.61 (3H, s), 1.43 (3H, d, J = 5.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 136.3, 131.3, 129.0, 128.5, 124.0, 92.3, 74.5, 73.6, 42.1, 23.2, 21.8, 21.1, 18.0; IR (neat): 3024 (w), 2990 (m), 2937 (m), 2919 (m), 2869 (w), 1515 (w), 1450 (w), 1406 (m), 1377 (w), 1172 (s), 1115 (s), 969 (s), 875 (w), 837 (w), 817 (m), 721 (w), 560 (w), 460 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{16}H_{26}NO_2$ $[M+NH_4]^+$: 264.1963, found: 264.1953.

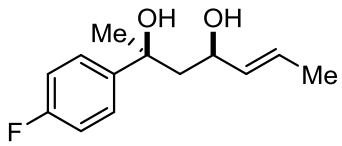


(2*S,4*R**,*E*)-2-(3-Fluorophenyl)hept-5-ene-2,4-diol (Table 4.2, entry 2)**. The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 69.1 mg (0.5 mmol) of 3′-fluoroacetophenone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.64** as a colorless oil (81.8 mg, 73% yield). R_f = 0.27 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.26 (1H, m), 7.22-7.19 (2H, m), 6.94-6.89 (1H, m), 5.69 (1H, dq, J = 15.5 Hz, 6.5 Hz), 5.46 (1H, dd, J = 15.0 Hz, 7.0 Hz), 4.53 (1H, br t, J = 8.0 Hz), 3.93 (1H, br s), 2.58 (1H, br s), 1.93 (1H, dd, J = 14.0 Hz, 9.5 Hz), 1.83 (1H, dd, J = 14.5 Hz, 3.0 Hz), 1.67 (3H, d, J = 6.5 Hz), 1.65 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.0 (d, $^1J_{CF}$ = 244.4 Hz), 152.1, 133.7, 129.7, 127.4, 120.2, 113.5 (d, $^2J_{CF}$ = 20.7 Hz), 111.9 (d, $^2J_{CF}$ = 22.5 Hz), 74.4, 71.2, 49.2, 28.3, 17.7; IR (neat): 3239 (br), 2940 (m), 2879 (m), 1614 (m), 1589 (s), 1485 (m), 1439 (s), 1377 (m), 1272 (m), 1252 (m), 1178 (m), 966 (s), 786 (m), 699 (s) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{21}FNO_2$ $[M+NH_4]^+$: 242.1556, found: 242.1565.

Proof of Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analysis of the spectral data, after conversion of the title compound **4.64** into **SI-3** as shown below.



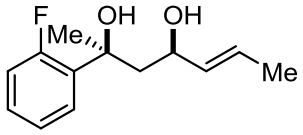
(2*S,4*S**,6*R**)-4-(3-Fluorophenyl)-2,4-dimethyl-6-((*E*)-prop-1-en-1-yl)-1,3-dioxane (SI-3)**. The acetonide (**SI-3**) was prepared in the same method as described for acetonide **SI-1**. R_f = 0.23 (9:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.27 (1H, m), 7.22-7.17 (2H, m), 6.94-6.90 (1H, m), 5.79 (1H, dq, *J* = 15.5 Hz, 6.0 Hz), 5.36 (1H, dd, *J* = 15.5 Hz, 8.5 Hz), 5.33 (1H, q, *J* = 5.0 Hz), 4.36-4.32 (1H, m), 1.81 (1H, dd, *J* = 13.0 Hz, 2.5 Hz), 1.74 (1H, dd, overlapped), 1.71 (3H, d, *J* = 6.5 Hz), 1.61 (3H, s), 1.44 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.0 (d, $^1J_{CF}$ = 244.4 Hz), 151.7, 131.0, 129.7, 128.7, 119.6, 113.6 (d, $^2J_{CF}$ = 21.1 Hz), 111.5 (d, $^2J_{CF}$ = 23.1 Hz), 92.4, 74.4, 73.5, 41.9, 23.2, 21.7, 17.9; IR (neat): 2989 (w), 2939 (w), 2873 (w), 1618 (w), 1589 (m), 1484 (w), 1437 (w), 1271 (m), 1156 (s), 1109 (s), 1040 (w), 968 (s), 899 (m), 864 (m), 784 (s), 744 (s), 482 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{15}H_{23}FNO_2$ $[M+NH_4]^+$: 268.1713, found: 268.1708.



(2*S,4*R**,*E*)-2-(4-Fluorophenyl)hept-5-ene-2,4-diol (Table 4.2, entry 3)**. The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of

P(*t*-Bu)$_3$, 69.1 mg (0.5 mmol) of 4′-fluoroacetophenone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.66** as a colorless oil (79.3 mg, 71% yield). R_f = 0.23 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43-7.41 (2H, m), 7.02-6.98 (2H, m), 5.68 (1H, dq, *J* = 15.0 Hz, 6.5 Hz), 5.46 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 4.52 (1H, br t, *J* = 7.5 Hz), 3.88 (1H, br s), 2.71 (1H, br s), 1.92 (1H, dd, *J* = 15.0 Hz, 10.5 Hz), 1.81 (1H, dd, *J* = 14.5 Hz, 2.5 Hz), 1.66 (3H, d, *J* = 6.0 Hz), 1.65 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.7 (d, $^1J_{CF}$ = 244.4 Hz), 145.0, 133.8, 127.3, 126.3, 114.9 (d, $^2J_{CF}$ = 21.2 Hz), 74.4, 71.2, 49.5, 28.3, 17.7; IR (neat): 3324 (br), 2941 (m), 2876 (m), 1602 (w), 1510 (s), 1420 (w), 1375 (w), 1223 (s), 1160 (m), 1090 (m), 1074 (w), 967 (m), 849 (m), 836 (s), 814 (w), 563 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{14}F$ $[M–2H_2O+H]^+$: 189.1080, found: 180.1083.

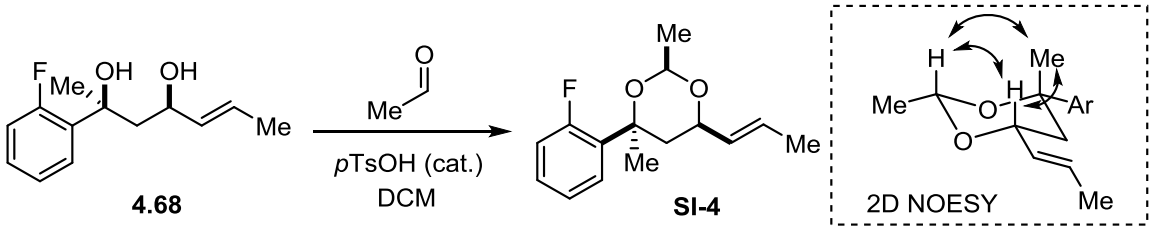
Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analogy.



(2*S,4*R**,*E*)-2-(2-Fluorophenyl)hept-5-ene-2,4-diol (Table 4.2, entry 4)**. The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 69.1 mg (0.5 mmol) of 2′-fluoroacetophenone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.68** as a colorless oil (70.9 mg, 63% yield). R_f = 0.31 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (1H, t, *J* = 8.0 Hz), 7.24-7.20 (1H, m), 7.14 (1H, t, *J* = 8.0 Hz), 7.00 (1H, dd, *J* = 12.0 Hz, 8.0 Hz), 5.68 (1H, dq, *J*

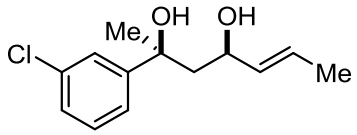
= 15.5 Hz, 7.0 Hz), 5.45 (1H, dd, J = 15.0 Hz, 7.0 Hz), 4.55 (1H, br t, J = 7.5 Hz), 3.99 (1H, br s), 2.47 (1H, br s), 2.17 (1H, dd, J = 14.5 Hz, 3.0 Hz), 1.99 (1H, dd, J = 15.0 Hz, 10.0 Hz), 1.70 (3H, s), 1.65 (3H, d, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.5 (d, $^1J_{CF}$ = 243.7 Hz), 135.6, 135.5, 133.7, 128.6, 127.1 (d, $^2J_{CF}$ = 21.6 Hz), 124.2, 116.0 (d, $^2J_{CF}$ = 24.0 Hz), 73.6, 71.1, 46.5, 27.5, 17.7; IR (neat): 3340 (br), 2972 (w), 2917 (w), 1614 (w), 1485 (m), 1448 (s), 1376 (w), 1214 (s), 1066 (m), 1037 (w), 965 (m), 818 (m), 757 (s), 447 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{14}F$ $[M–2H_2O+H]^+$: 189.1079, found: 189.1074.

Proof of Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analysis of the spectral data, after conversion of the title compound **4.68** into **SI-4** as shown below.



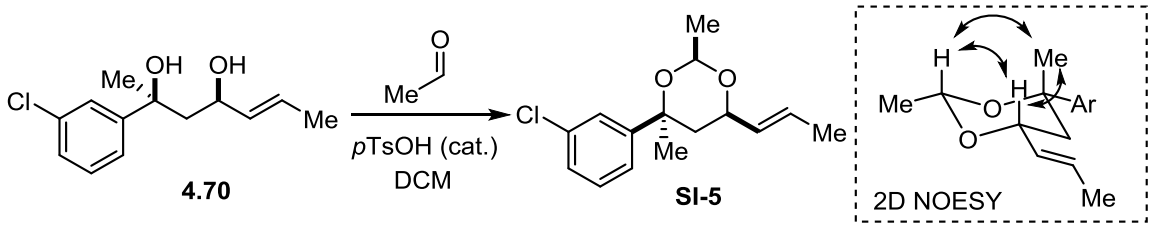
(2*S,4*S**,6*R**)-4-(2-Fluorophenyl)-2,4-dimethyl-6-((*E*)-prop-1-en-1-yl)-1,3-dioxane (SI-4)**. The acetonide (**SI-4**) was prepared in the same method as described for acetonide **SI-1**. R_f = 0.33 (9:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (1H, t, J = 8.0 Hz), 7.23-7.19 (1H, m), 7.13 (1H, t, J = 7.5 Hz), 6.98 (1H, dd, J = 12.0 Hz, 8.0 Hz), 5.78 (1H, dq, J = 15.0 Hz, 6.5 Hz), 5.46 (1H, dd, J = 15.5 Hz, 7.0 Hz), 5.26 (1H, q, J = 5.0 Hz), 4.37-4.33 (1H, m), 2.21 (1H, dd, J = 13.5 Hz, 2.5 Hz), 1.71 (1H, dd, overlapped), 1.69 (3H, d, J = 6.5 Hz), 1.69 (3H, s), 1.45 (3H, d, J = 5.0 Hz); ^{13}C NMR (125 MHz,

$CDCl_3$): δ 159.4 (d, $^1J_{CF}$ = 245.5 Hz), 135.5, 135.4, 131.1, 128.4 (d, $^2J_{CF}$ = 22.2 Hz), 126.4, 124.1, 115.9 (d, $^2J_{CF}$ = 23.2 Hz), 91.9, 73.5, 73.2, 40.0, 21.8, 21.7, 17.9; IR (neat): 3089 (w), 2991 (w), 2876 (w), 1678 (w), 1616 (w), 1581 (m), 1488 (s), 1449 (w), 1125 (s), 1110 (s), 1069 (w), 1037 (m), 971 (s), 879 (w), 804 (m), 758 (s), 498 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{15}H_{23}FNO_2$ $[M+NH_4]^+$: 268.1713, found: 268.1722.

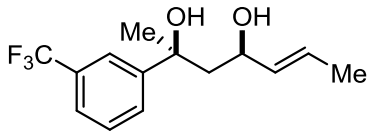


(2*S,4*R**,*E*)-2-(3-Chlorophenyl)hept-5-ene-2,4-diol (Table 4.2, entry 5)**. The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 77.3 mg (0.5 mmol) of 3′-chloroacetophenone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.70** as a colorless oil (75.5 mg, 63% yield). R_f = 0.33 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (1H, t, *J* = 2.0 Hz), 7.33 (1H, dt, *J* = 8.0 Hz, 2.0 Hz), 7.26 (1H, t, *J* = 8.0 Hz), 7.20 (1H, d, *J* = 8.0 Hz), 5.69 (1H, dq, *J* = 15.5 Hz, 6.5 Hz), 5.46 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 4.53 (1H, br t, *J* = 8.5 Hz), 3.94 (1H, br s), 2.50 (1H, br s), 1.93 (1H, dd, *J* = 15.0 Hz, 10.0 Hz), 1.83 (1H, dd, *J* = 15.0 Hz, 3.0 Hz), 1.67 (3H, d, *J* = 6.5 Hz), 1.64 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.4, 134.3, 133.7, 129.6, 127.4, 126.8, 125.1, 122.8, 74.4, 71.1, 49.1, 28.2, 17.7; IR (neat): 3320 (br), 2977 (m), 2897 (m), 1596 (w), 1571 (w), 1421 (s), 1376 (w), 1212 (m), 1142 (w), 1112 (w), 1080 (m), 965 (s), 894 (w), 850 (w), 785 (s), 699 (s), 495 (w), 406 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{14}Cl$ $[M–2H_2O+H]^+$: 205.0784, found: 205.0784.

Proof of Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analysis of the spectral data, after conversion of the title compound **4.70** into **SI-**5 as shown below.



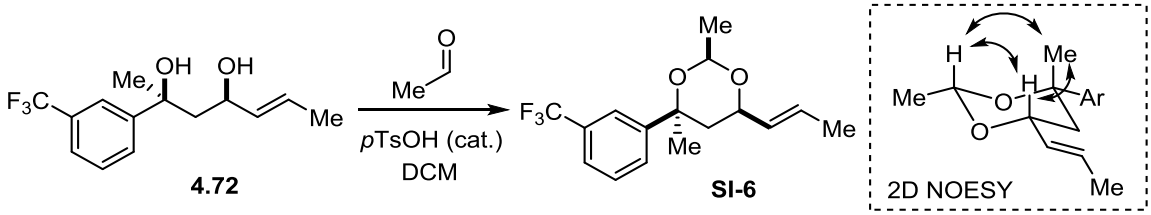
(2*S,4*S**,6*R**)-4-(3-Chlorophenyl)-2,4-dimethyl-6-((*E*)-prop-1-en-1-yl)-1,3-dioxane (SI-5)**. The acetonide (**SI-5**) was prepared in the same method as described for acetonide **SI-1**. R_f = 0.28 (9:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (1H, t, *J* = 1.5 Hz), 7.31 (1H, d, *J* = 7.5 Hz), 7.26 (1H, t, *J* = 8.0 Hz), 7.21 (1H, d, *J* = 7.5 Hz), 5.79 (1H, dq, *J* = 15.5 Hz, 7.0 Hz), 5.48 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 5.22 (1H, q, *J* = 5.0 Hz), 4.35-4.31 (1H, m), 1.80 (1H, dd, *J* = 13.5 Hz, 2.5 Hz), 1.71 (1H, dd, overlapped), 1.70 (3H, d, *J* = 6.5 Hz), 1.61 (3H, s), 1.44 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.0, 134.3, 131.0, 129.6, 128.7, 127.0, 124.6, 122.3, 92.4, 74.4, 73.5, 41.9, 23.3, 21.7, 17.9; IR (neat): 2990 (w), 2938 (w), 2918 (w), 2876 (w), 1597 (w), 1572 (w), 1474 (w), 1419 (m), 1407 (m), 1223 (w), 1173 (s), 1124 (s), 1081 (w), 971 (s), 879 (w), 847 (w), 785 (m), 697 (s), 610 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{15}H_{23}ClNO_2$ $[M+NH_4]^+$: 284.1417, found: 284.1410.



(2*S,4*R**,*E*)-2-(3-(Trifluoromethyl)phenyl)hept-5-ene-2,4-diol (Table 4.2, entry 6)**. The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg

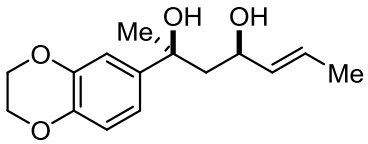
(0.075 mmol) of P(*t*-Bu)$_3$, 94.1 mg (0.5 mmol) of 3′-(trifluoromethyl)- acetophenone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.72** as a colorless oil (96.3 mg, 70% yield). R_f = 0.27 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (1H, s), 7.64 (1H, d, *J* = 8.0 Hz), 7.49 (1H, d, *J* = 7.5 Hz), 7.44 (1H, t, *J* = 7.5 Hz), 5.69 (1H, dq, *J* = 15.5 Hz, 6.5 Hz), 5.46 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 4.56 (1H, br t, *J* = 8.0 Hz), 4.19 (1H, br s), 2.50 (1H, br s), 1.94 (1H, dd, *J* = 14.5 Hz, 10.0 Hz), 1.85 (1H, dd, *J* = 15.0 Hz, 3.0 Hz), 1.68 (3H, s), 1.66 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.3, 133.6, 130.6 (q, $^2J_{CF}$ = 31.8 Hz), 128.7, 128.1, 127.7, 124.0 (q, $^1J_{CF}$ = 272.1 Hz), 123.6 (q, $^3J_{CF}$ = 3.6 Hz), 121.6 (q, $^3J_{CF}$ = 3.6 Hz), 74.4, 71.3, 49.2, 28.2, 17.7; IR (neat): 3333 (br), 2976 (m), 2919 (m), 1438 (w), 1377 (w), 1328 (s), 1207 (w), 1164 (s), 1122 (s), 1072 (m), 966 (w), 899 (w), 852 (w), 804 (w), 730 (w), 704 (m), 657 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{21}FNO_2$ $[M+NH_4]^+$: 292.1524, found: 292.1525.

Proof of Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analysis of the spectral data, after conversion of the title compound **4.72** into **SI-6** as shown below.



(2*S,4*S**,6*R**)-2,4-Dimethyl-6-((*E*)-prop-1-en-1-yl)-4-(3-(trifluoromethyl)phenyl)-1,3-dioxane (SI-6)**. The acetonide (**SI-6**) was prepared in the same method as described

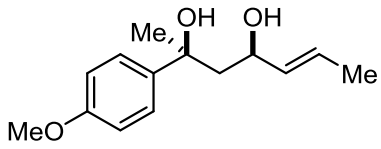
for acetonide **SI-1**. R_f = 0.23 (9:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (1H, s), 7.64 (1H, d, *J* = 7.5 Hz), 7.50 (1H, d, *J* = 7.5 Hz), 7.45 (1H, t, *J* = 7.5 Hz), 5.80 (1H, dq, *J* = 15.0 Hz, 6.5 Hz), 5.48 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 5.25 (1H, q, *J* = 5.0 Hz), 4.38-4.35 (1H, m), 1.85 (1H, dd, *J* = 13.5 Hz, 2.5 Hz), 1.72 (1H, dd, overlapped), 1.71 (3H, d, *J* = 6.5 Hz), 1.64 (3H, s), 1.45 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.9, 130.9, 130.6 (q, $^2J_{CF}$ = 31.8 Hz), 128.8 (2 C′s), 127.6, 124.4 (q, $^1J_{CF}$ = 272.5 Hz), 123.7 (q, $^3J_{CF}$ = 3.6 Hz), 121.1 (q, $^3J_{CF}$ = 3.6 Hz), 92.4, 74.4, 73.4, 41.8, 23.3, 21.7, 18.0; IR (neat): 2990 (w), 2940 (w), 2921 (w), 2878 (w), 1440 (w), 1333 (s), 1287 (w), 1220 (w), 1165 (s), 1125 (s), 1072 (m), 971 (m), 804 (w), 703 (m), 656 (w), 611 (w), 546 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{16}H_{23}F_3NO_2$ $[M+NH_4]^+$: 318.1681, found: 318.1694.



(2*S,4*R**,*E*)-2-(2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)hept-5-ene-2,4-diol (Table 4.2, entry 7).** The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 89.1 mg (0.5 mmol) of 1,4-benzodioxan-6-yl methyl ketone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.74** as a colorless oil (90.9 mg, 69% yield). R_f = 0.28 (1:2 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.98 (1H, s), 6.91 (1H, d, *J* = 9.0 Hz), 6.82 (1H, d, *J* = 8.5 Hz), 5.67 (1H, dq, *J* = 15.5 Hz, 6.5 Hz), 5.46 (1H, dd, *J* = 15.0 Hz, 7.0 Hz), 4.49 (1H, br t, *J* = 8.5 Hz), 4.25 (4H, s), 3.38 (1H, br s), 2.80 (1H, br s), 1.93 (1H, dd, *J* = 15.0 Hz, 10.0 Hz), 1.80 (1H, dd, *J* = 15.0 Hz, 2.5 Hz), 1.67 (3H, d, *J* = 6.0 Hz), 1.63 (3H, s); ^{13}C NMR (125 MHz,

$CDCl_3$): δ 143.2, 142.8, 142.3, 133.9, 127.0, 117.6, 117.0, 113.8, 74.5, 71.0, 64.5 (2 C′s), 49.5, 28.3, 17.8; IR (neat): 3412 (br), 2996 (m), 2930 (w), 2854 (w), 1590 (w), 1505 (s), 1460 (w), 1424 (m), 1377 (m), 1309 (m), 1285 (s), 1258 (m), 1175 (w), 1126 (m), 1100 (w), 1068 (s), 949 (w), 887 (w), 642 (w), 496 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{15}H_{17}O_2$ $[M–2H_2O+H]^+$: 229.1228, found: 229.1228.

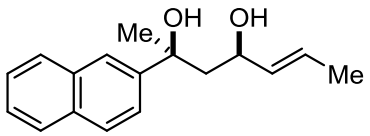
Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analogy.



(2*S,4*R**,*E*)-2-(4-Methoxyphenyl)hept-5-ene-2,4-diol (Table 4.2, entry 8).** The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 75.1 mg (0.5 mmol) of 4′-methoxylacetophenone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.76** as a colorless oil (61.3 mg, 52% yield). R_f = 0.31 (1:2 hexanes:Et_2O); ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 (2H, d, *J* = 9.0 Hz), 6.87 (2H, d, *J* = 9.0 Hz), 5.69 (1H, dq, *J* = 15.0 Hz, 6.5 Hz), 5.48 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 4.51 (1H, br t, *J* = 7.5 Hz), 3.80 (3H, s), 3.35 (1H, br s), 2.72 (1H, br s), 1.96 (1H, dd, *J* = 14.5 Hz, 10.0 Hz), 1.83 (1H, dd, *J* = 15.0 Hz, 3.0 Hz), 1.68 (3H, d, *J* = 6.5 Hz), 1.66 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 141.5, 134.0, 127.0, 125.7, 113.7, 74.6, 71.1, 55.4, 49.7, 28.4, 17.8; IR (neat): 3372 (br), 2938 (w), 2916 (w), 2854 (w), 1611 (w), 1512 (s), 1459 (w), 1442 (w), 1416 (w), 1302 (m), 1249 (s), 1215 (w), 1179 (s), 1094 (m), 1074 (w), 1035 (m), 966 (m),

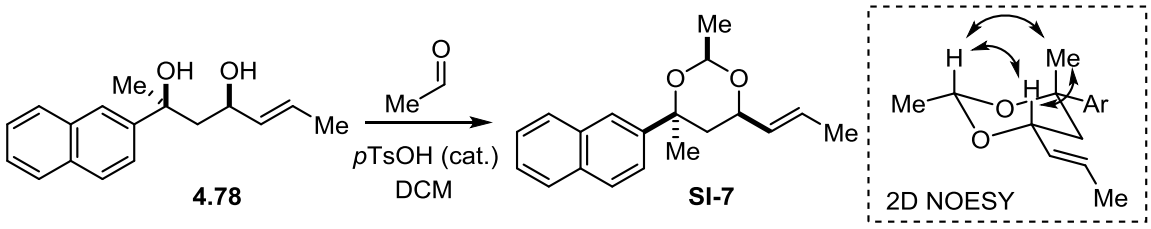
847 (m), 832 (m), 802 (w), 491 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{14}H_{19}O_2$ [M–H_2O+H]$^+$: 219.1385, found: 219.1386.

Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analogy.

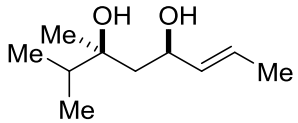


(2*S,4*R**,*E*)-2-(Naphthalen-2-yl)hept-5-ene-2,4-diol (Table 4.2, entry 9)**. The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 85.1 mg (0.5 mmol) of 2′-acetonaphthone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford **4.78** (92.4 mg, 72% yield). R_f = 0.24 (1:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (1H, s), 7.85-7.81 (3H, m), 7.56 (1H, dd, *J* = 8.5 Hz, 2.0 Hz), 7.49-7.44 (2H, m), 5.70 (1H, dq, *J* = 15.5 Hz, 6.5 Hz), 5.50 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 4.58 (1H, br t, *J* = 9.0 Hz), 3.71 (1H, br s), 2.64 (1H, br s), 2.06 (1H, dd, *J* = 14.5 Hz, 10.0 Hz), 1.97 (1H, dd, *J* = 15.0 Hz, 3.5 Hz), 1.76 (3H, s), 1.67 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.5, 133.9, 133.4, 132.4, 128.4, 128.1, 127.6, 127.3, 126.2, 125.8, 123.5, 122.8, 74.9, 71.2, 49.3, 28.5, 17.7; IR (neat): 3325 (br), 3022 (w), 2938 (w), 2853 (w), 1600 (w), 1506 (w), 1450 (m), 1435 (m), 1420 (m), 1376 (m), 1186 (m), 1128 (s), 965 (m), 922 (w), 902 (w), 860 (s), 820 (s), 747 (s), 479 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{17}H_{17}O$ [M–2H_2O+H]$^+$: 237.1279, found: 237.1283.

Proof of Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analysis of the spectral data, after conversion of the title compound (**4.78**) into **SI-7** as shown below.



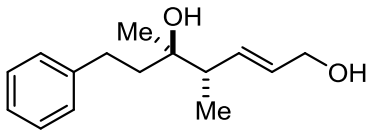
(2*S,4*S**,6*R**)-2,4-Dimethyl-4-(naphthalen-2-yl)-6-((*E*)-prop-1-en-1-yl)-1,3-dioxane (SI-7)**. The acetonide (**SI-7**) was prepared in the same method as described for acetonide **SI-1**. R_f = 0.22 (9:1 hexanes:Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (1H, s), 7.86-7.82 (3H, m), 7.59 (1H, dd, *J* = 8.5 Hz, 2.0 Hz), 7.49-7.44 (2H, m), 5.83 (1H, dq, *J* = 15.0 Hz, 6.5 Hz), 5.52 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 5.32 (1H, q, *J* = 5.0 Hz), 4.44-4.40 (1H, m), 1.94 (1H, dd, *J* = 13.5 Hz, 2.5 Hz), 1.86 (1H, dd, *J* = 13.0 Hz, *J* = 11.5 Hz), 1.73 (3H, d, overlapped), 1.72 (3H, s), 1.51 (3H, d, *J* = 5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.2, 133.3, 132.5, 131.2, 128.6, 128.4, 128.0, 127.6, 126.0, 125.8, 123.0, 122.4, 92.4, 74.8, 73.6, 42.0, 23.2, 21.8, 18.0; IR (neat): 2987 (w), 2936 (w), 2917 (w), 2869 (w), 1405 (m), 1378 (m), 1163 (m), 1128 (s), 1108 (s), 1040 (w), 966 (s), 935 (m), 856 (m), 817 (m), 746 (s), 663 (w), 652 (w), 478 (s) cm^{-1}; HRMS (ESI+) calculated for $C_{19}H_{26}NO_2$ $[M+NH_4]^+$: 300.1963, found: 300.1953.



(3*S*,5*R*,*E*)-2,3-Dimethyloct-6-ene-3,5-diol (Table 2.4, entry 11) The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.3 mg (0.075 mmol) of P(t-Bu)$_3$, 49.0 mg (0.5 mmol) of 3-methylbutan-2-one, 68.0 mg (1.0 mmol) of *trans*-1,3-pentadiene,

and 253.0 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.82** as a colorless liquid (47 mg, 51% yield). R_f = 0.49 (1:2 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.57 (1H, qn, *J* = 7.5 Hz), 5.56 (1H, dd, *J* = 15.5 Hz, 6.5 Hz), 4.25 (1H, qn, *J* = 6.5 Hz), 2.17 (1H, dd, *J* = 7.5 Hz, 7.0 Hz), 2.10 (1H, dd, *J*=7.5 Hz, 7.0 Hz), 1.62 (1H, m), 1.53 (1H, br s), 1.21 (3H, d, *J* = 6.5 Hz), 1.01 (3H, s), 0.86 (3H, d, *J* = 6.5 Hz), 0.84 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 125.8, 77.6, 68.9, 42.4, 37.0, 23.3, 23.0, 17.7, 17.0; IR (neat): 3371 (br), 2969 (s), 2931 (s), 2877 (m), 1454 (w), 1385 (m), 1370 (m), 1218 (w), 1154 (w), 1063 (m), 974 (m), 927 (w), 862 (w), 612 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{10}H_{20}O_2$ $[M+H^+]^+$: 173.1541, found: 173.1540.

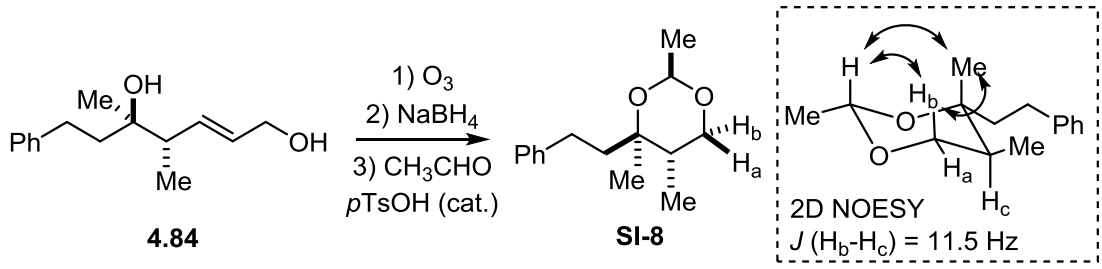
Proof of Stereochemistry. The relative configuration was assigned as *syn* (C_2-C_4) by analogy.



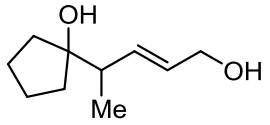
(4*S,5*R**,*E*)-4,5-Dimethyl-7-phenylhept-2-ene-1,5-diol (Table 4.3, entry 1)**. The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 74.1 mg (0.5 mmol) of benzylacetone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.84** as a colorless oil (80.5 mg, 69% yield). R_f = 0.59 (1:2 hexanes:EtOAc); ^{1}H NMR (500 MHz, C_6D_6): δ 7.19-7.12 (4H, m), 7.08-7.04 (1H, m), 5.67 (1H, dd, *J* = 15.5 Hz, 8.0 Hz), 5.58 (1H, dt, *J* = 15.0 Hz, 5.0 H), 3.95 (1H, dd, *J* = 9.0 Hz, 5.0 Hz), 3.92 (1H, dd, *J* = 9.0 Hz, 5.0 Hz), 2.78 (1H, br), 2.70

(2H, t, J = 7.5 Hz), 2.35 (1H, br), 2.20 (1H, qn, J = 7.0 Hz), 1.71 (2H, m), 1.02 (3H, s), 0.88 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 133.9, 131.2, 128.6, 128.5, 125.9, 74.1, 63.6, 46.1, 42.3, 29.9, 23.6, 15.5; IR (neat): 3356 (br), 2970 (m), 2934 (m), 1454 (m), 1378 (m), 1090 (w), 1068 (w), 999 (s), 974 (w), 754 (w), 735 (m), 698 (s) cm^{-1}; HRMS (ESI+) calculated for $C_{15}H_{26}NO_2$ $[M+NH_4]^+$: 252.1964, found: 252.1963.

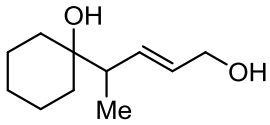
Proof of Stereochemistry. The relative configuration was determined by analysis of the spectral data, after conversion of the title compound **4.84** into **SI-8** by ozonolysis, reduction, and acetonide synthesis as illustrated below.



(2*S,4*R**,5*S**)-2,4,5-Trimethyl-4-phenethyl-1,3-dioxane (SI-8)**. R_f = 0.78 (5:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.27 (2H, t, J = 7.5 Hz), 7.24-7.22 (2H, d, J = 7.0 Hz), 7.19-7.16 (1H, t, J = 7.5 Hz), 4.94 (1H, q, J = 4.5 Hz), 3.74 (1H, dd, J = 11.5 Hz, 5.0 Hz), 3.55 (1H, t, J = 11.5 Hz), 2.80 (1H, td, 13.5 Hz, 5.0 Hz), 2.72 (1H, td, J = 13.5 Hz, 5.5 Hz), 2.09-2.02 (1H, m), 1.88-1.75 (2H, m), 1.30 (3H, d, J = 5.0 Hz), 1.20 (3H, s), 0.72 (3H, d, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 128.6, 128.4, 125.7, 92.5, 76.5, 68.5, 43.4, 36.2, 28.8, 21.6, 16.4, 11.9; IR (neat): 2959 (m), 2938 (m), 2857 (w), 1454 (w), 1402 (s), 1386 (w), 1374 (w), 1149 (s), 1119 (s), 1095 (m), 1038 (w), 973 (w), 947 (w), 848 (w), 754 (w), 698 (m) cm^{-1}; HRMS (ESI+) calculated for $C_{15}H_{23}O_2$ $[M+H]^+$: 235.1698, found: 235.1687.

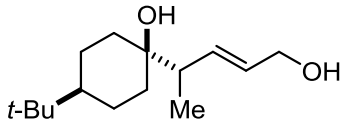


(*E*)-1-(5-Hydroxypent-3-en-2-yl)cyclopentanol (Table 4.3, entry 2). The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 42.0 mg (0.5 mmol) of cyclopentanone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.86** as a colorless oil (47.3 mg, 56% yield). R_f = 0.35 (1:2 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 (1H, dd, *J* = 15.5 Hz, 7.5 Hz), 5.68 (1H, dt, *J* = 15.5 Hz, 5.5 Hz), 4.10 (2H, d, *J* = 5.0 Hz), 2.25 (1H, qn, *J* = 7.0 Hz), 1.90 (1H, br) 1.83-1.74 (2H, m), 1.62-1.53 (6H, m), 1.05 (3H, d, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7, 130.1, 84.4, 63.5, 45.7, 38.6, 37.7, 24.0, 23.9, 15.3; IR (neat): 3341 (br), 2960 (w), 2871 (w), 1453 (w), 1372 (w), 1326 (w), 1194 (w), 1124 (w), 1088 (m), 1051 (w), 971 (s), 809 (w), 700 (w), 638 (m), 500 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{10}H_{22}NO_2$ $[M+NH_4]^+$: 188.1650, found: 188.1657.



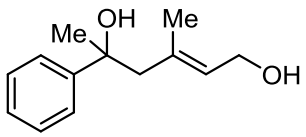
(*E*)-1-(5-Hydroxypent-3-en-2-yl)cyclohexanol (Table 4.3, entry 3). The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 49.0 mg (0.5 mmol) of cyclohexanone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.88** as a colorless oil (47.8 mg, 52% yield). R_f = 0.49 (1:2 hexanes:EtOAc); ^{1}H NMR (500 MHz, C_6D_6): δ 5.59 (1H, dd, *J* = 15.5 Hz), 5.47 (1H, dt, *J* = 15.0 Hz, 5.5 Hz), 3.84 (2H, d, *J* = 6.0 Hz), 1.96 (1H, m), 1.66-1.53 (3H, m), 1.45-1.35 (4H, m), 1.23-1.16 (2H, m), 1.15-1.01 (1H, m), 0.95 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100

MHz, $CDCl_3$): δ 134.2, 130.2, 72.5, 63.6, 35.2, 34.4, 25.7, 21.7, 14.3; IR (neat): 3354 (br), 2931 (s), 2858 (m), 1448 (w), 1373 (w), 1256 (w), 1164 (w), 1139 (w), 1080 (w), 1002 (m), 972 (s), 664 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{11}H_{24}NO_2$ $[M+NH_4]^+$: 202.1807, found: 202.1800.



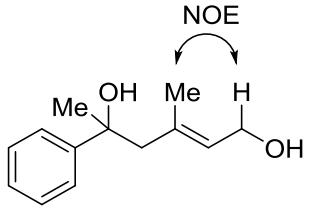
(*E*)-4-(*tert*-Butyl)-1-(5-hydroxypent-3-en-2-yl)cyclohexanol (Table 4.3, entry 4). The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of P(*t*-Bu)$_3$, 77.0 mg (0.5 mmol) of 4-*tert*-butylcyclohexanone, 68.1 mg (1.0 mmol) of *trans*-1,3-pentadiene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.90** as a colorless oil (64.0 mg, 53% yield). R_f = 0.56 (1:2 hexanes:EtOAc); ^{1}H NMR (500 MHz, C_6D_6): δ 5.65 (1H, ddt, *J* = 15.0 Hz, 8.5 Hz, 1.2 Hz), 5.54 (1H, dt, *J* = 15.0 Hz, 5.5 Hz), 3.92 (2H, dd, *J* = 5.5 Hz, 1.2 Hz), 1.97 (1H, m), 1.62-1.40 (7H, m), 1.17 (2H, tt, *J* = 13.0 Hz, 4.0 Hz), 0.99 (3H, d, *J* = 6.8 Hz), 0.91 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 130.5, 72.3, 63.8, 48.0, 47.9, 35.2, 34.7, 32.5, 27.7, 22.6, 22.5, 14.7; IR (neat): 3346 (br), 2939 (s), 2866 (m), 1666 (w), 1461 (w), 1442 (w), 1392 (w), 1364 (m), 1316 (w), 1235 (w), 1190 (w), 1140 (w), 1118 (w), 1091 (w), 1050 (w), 1003 (m), 973 (s), 915 (w), 890 (w), 828 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{15}H_{32}NO_2$ $[M+NH_4]^+$: 258.2433, found: 258.2437.

Stereochemistry. The relative configuration was assigned as *syn* (C_1-C_4) by analysis of the ^{13}C NMR spectrum based on the NMR studies of related compounds.[22]



(*E*)-3-Methyl-5-phenylhex-2-ene-1,5-diol (Scheme 4.9). The reaction was performed according to the general procedure with 13.8 mg (0.05 mmol) of $Ni(cod)_2$, 15.2 mg (0.075 mmol) of $P(t\text{-}Bu)_3$, 60.1 mg (0.5 mmol) of acetophenone, 68.1 mg (1.0 mmol) of isoprene, and 253.9 mg (1.0 mmol) of $B_2(pin)_2$ in THF (2.5 mL) for 48 h, followed by oxidation, to afford the title compound **4.92** as a colorless oil (40.1 mg, 39% yield). R_f = 0.28 (1:2 hexanes:EtOAc); ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (2H, d, *J* = 7.0 Hz), 7.34 (2H, d, *J* = 7.0 Hz), 7.24 (1H, t, *J* = 7.0 Hz), 5.34 (1H, t, *J* = 7.5 Hz), 3.97 (2H, s), 2.60 (2H, d, *J* = 8.0 Hz), 1.95 (1H, br s), 1.64 (3H, s), 1.57 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 139.1, 128.3, 126.8, 124.9, 120.4, 74.7, 68.8, 42.1, 30.0, 14.1; IR (neat): 3357 (br), 2965 (m), 2846 (m), 2792 (w), 1494 (w), 1446 (s), 1373 (m), 1286 (w), 1218 (w), 1068 (m), 1028 (m), 1013 (m), 950 (w), 880 (w), 764 (s), 700 (s), 623 (w), 555 (w) cm^{-1}; HRMS (ESI+) calculated for $C_{13}H_{22}NO_2$ $[M+NH_4]^+$: 224.1650, found: 224.1645.

Stereochemistry: The alkene configuration was assigned as *E* by NOESY analysis.



[22] (a) Trost, B. M.; Florez, J.; Jebaratnam, D. J. *J. Am. Chem. Soc*. **1987**, *109*, 613. (b) Trost, B. M.; Florez, J.; Haller, K. J. *J. Org. Chem*. **1988**, *53*, 2394. (c) Lindsay, H, A.; Salisbury, C. L.; Cordes, W.; McIntosh, M. C. *Org. Lett*. **2001**, *3*, 4007.